MEDMAPS FOR

Pathophysiology

SMTEBOOKS

- Concept maps of classic disease processes and mechanisms
- Two-page layouts that encourage interactive study
- Excellent review for basic science courses and USMLE Step 1

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Wolters Kluwer Health | Lippincott Williams & Wilkins

thePoint

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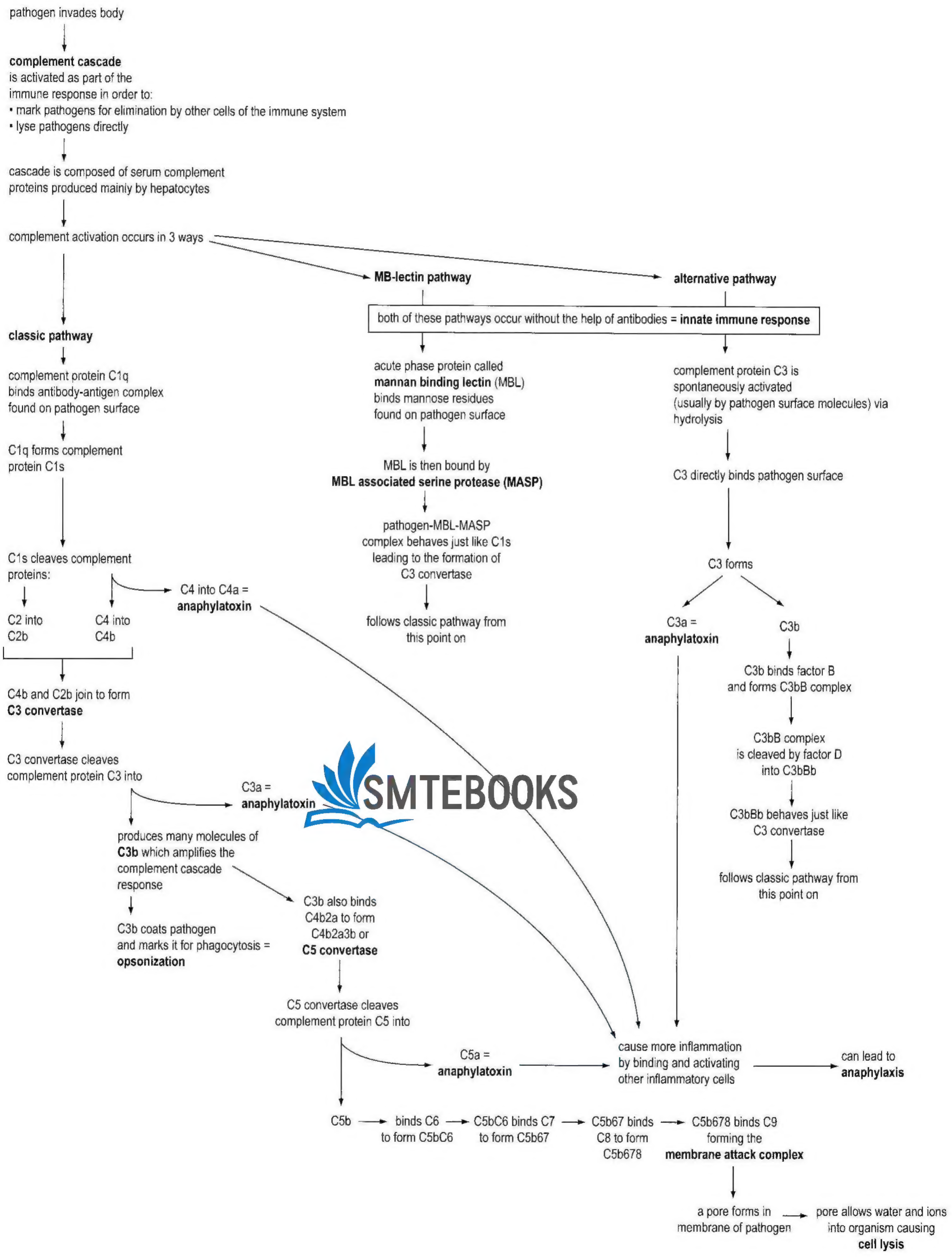
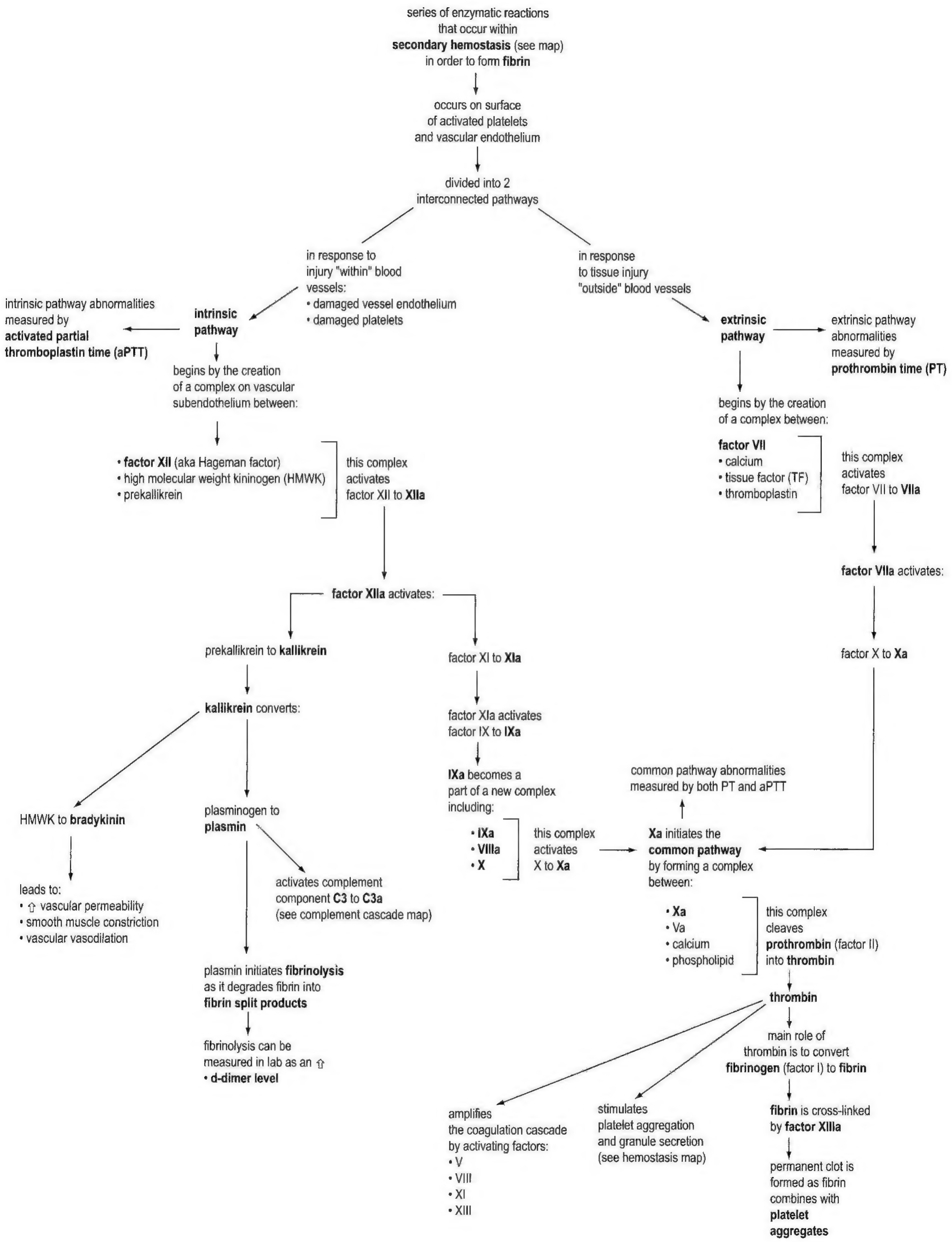

pathogen invades body
complement cascade is activated as part of the immune response in order to:
• mark pathogens for elimination by other cells of the immune system
• lyse pathogens directly
cascade is composed of serum complement proteins produced mainly by hepatocytes
complement activation occurs in 3 ways
classic pathway
complement protein C1q binds antibody-antigen complex found on pathogen surface
C1q forms complement protein C1s
C1s cleaves complement proteins:
C2 into C2b
C4 into C4b
C4 into C4a = **anaphylatoxin**
C4b and C2b join to form **C3 convertase**
C3 convertase cleaves complement protein C3 into
C3a = **anaphylatoxin**
produces many molecules of **C3b** which amplifies the complement cascade response
C3b coats pathogen and marks it for phagocytosis = **opsonization**
C3b also binds C4b2a to form C4b2a3b or **C5 convertase**
C5 convertase cleaves complement protein C5 into
C5a = **anaphylatoxin**
C5b
binds C6 to form C5bC6
C5bC6 binds C7 to form C5b67
C5b67 binds C8 to form C5b678
C5b678 binds C9 forming the **membrane attack complex**
a pore forms in membrane of pathogen
pore allows water and ions into organism causing **cell lysis**
MB-lectin pathway
alternative pathway
both of these pathways occur without the help of antibodies = **innate immune response**
acute phase protein called **mannan binding lectin** (MBL) binds mannose residues found on pathogen surface
MBL is then bound by **MBL associated serine protease (MASP)**
pathogen-MBL-MASP complex behaves just like C1s leading to the formation of C3 convertase
follows classic pathway from this point on
complement protein C3 is spontaneously activated (usually by pathogen surface molecules) via hydrolysis
C3 directly binds pathogen surface
C3 forms
C3a = **anaphylatoxin**
C3b
C3b binds factor B and forms C3bB complex
C3bB complex is cleaved by factor D into C3bBb
C3bBb behaves just like C3 convertase
follows classic pathway from this point on
cause more inflammation by binding and activating other inflammatory cells
can lead to **anaphylaxis**

SMTEBOOKS



series of enzymatic reactions that occur within **secondary hemostasis** (see map) in order to form **fibrin**

occurs on surface of activated platelets and vascular endothelium

divided into 2 interconnected pathways

in response to injury "within" blood vessels:
- damaged vessel endothelium
- damaged platelets

intrinsic pathway

intrinsic pathway abnormalities measured by **activated partial thromboplastin time (aPTT)**

begins by the creation of a complex on vascular subendothelium between:
- **factor XII** (aka Hageman factor)
- high molecular weight kininogen (HMWK)
- prekallikrein

this complex activates factor XII to **XIIa**

factor XIIa activates:

prekallikrein to **kallikrein**

kallikrein converts:

HMWK to **bradykinin**

leads to:
- ⇧ vascular permeability
- smooth muscle constriction
- vascular vasodilation

plasminogen to **plasmin**

activates complement component **C3** to **C3a** (see complement cascade map)

plasmin initiates **fibrinolysis** as it degrades fibrin into **fibrin split products**

fibrinolysis can be measured in lab as an ⇧
- **d-dimer level**

factor XI to **XIa**

factor XIa activates factor IX to **IXa**

IXa becomes a part of a new complex including:
- **IXa**
- **VIIIa**
- **X**

this complex activates X to **Xa**

in response to tissue injury "outside" blood vessels

extrinsic pathway

extrinsic pathway abnormalities measured by **prothrombin time (PT)**

begins by the creation of a complex between:

factor VII
- calcium
- tissue factor (TF)
- thromboplastin

this complex activates factor VII to **VIIa**

factor VIIa activates:

factor X to **Xa**

Xa initiates the **common pathway** by forming a complex between:
- **Xa**
- Va
- calcium
- phospholipid

common pathway abnormalities measured by both PT and aPTT

this complex cleaves **prothrombin** (factor II) into **thrombin**

thrombin

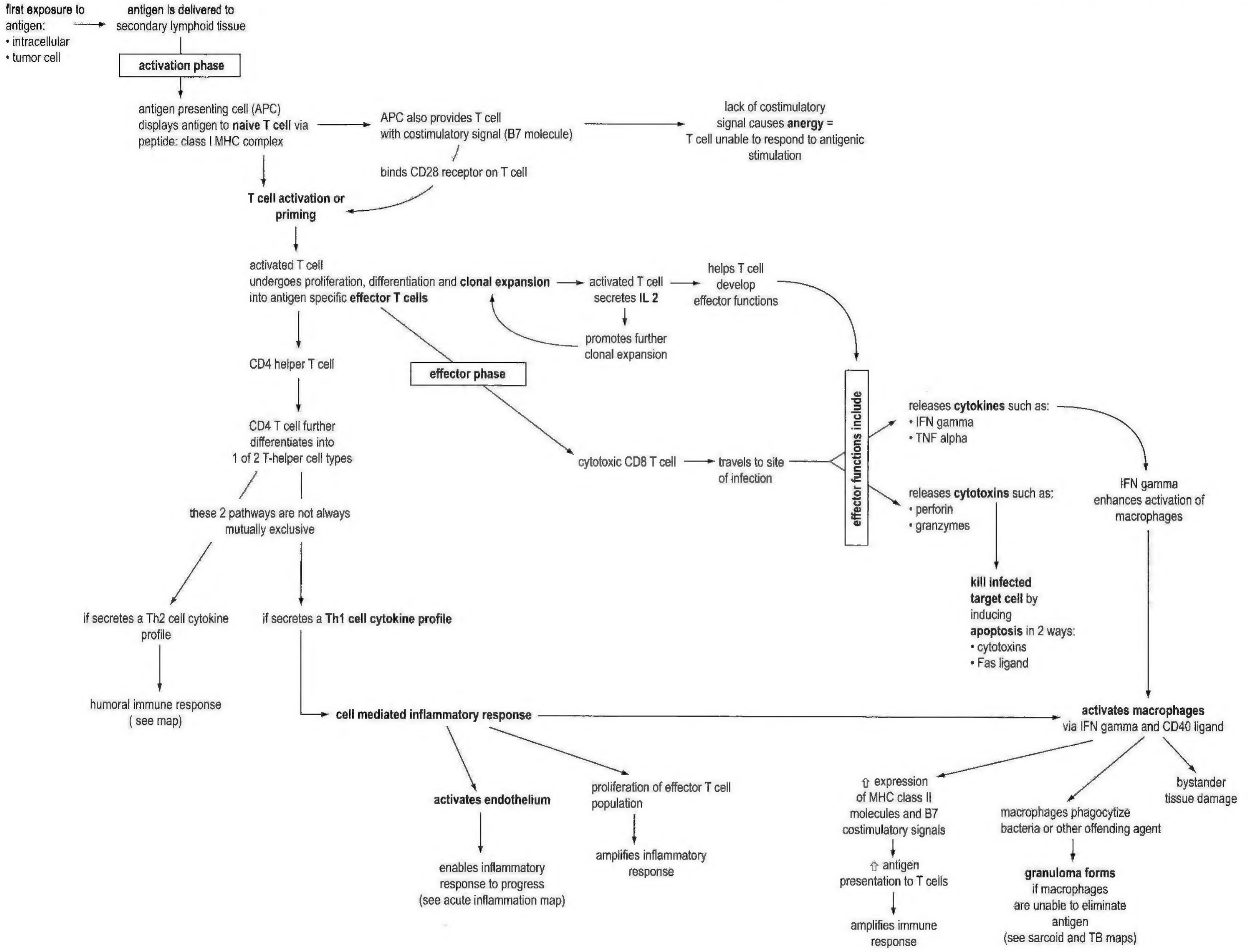
amplifies the coagulation cascade by activating factors:
- V
- VIII
- XI
- XIII

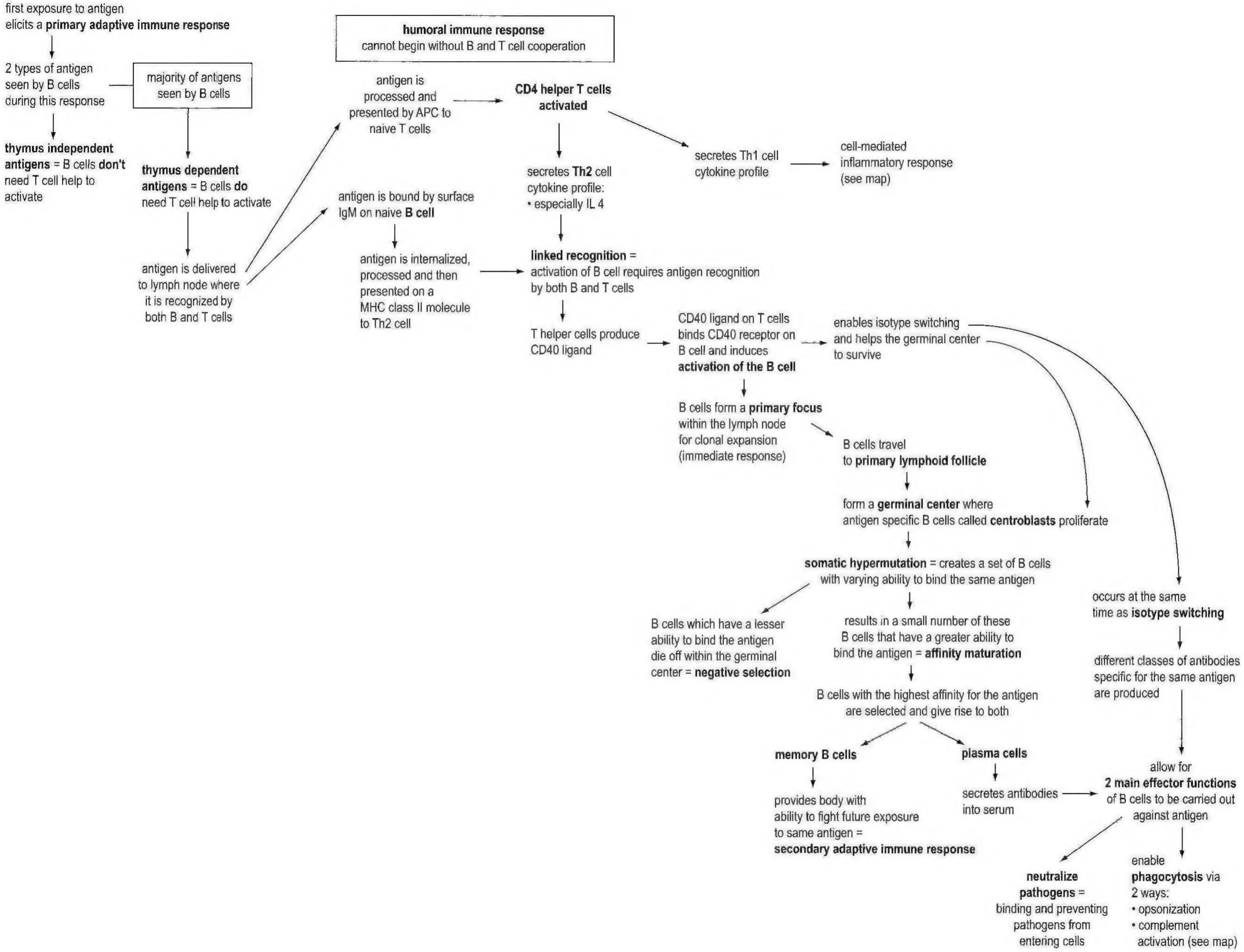
stimulates platelet aggregation and granule secretion (see hemostasis map)

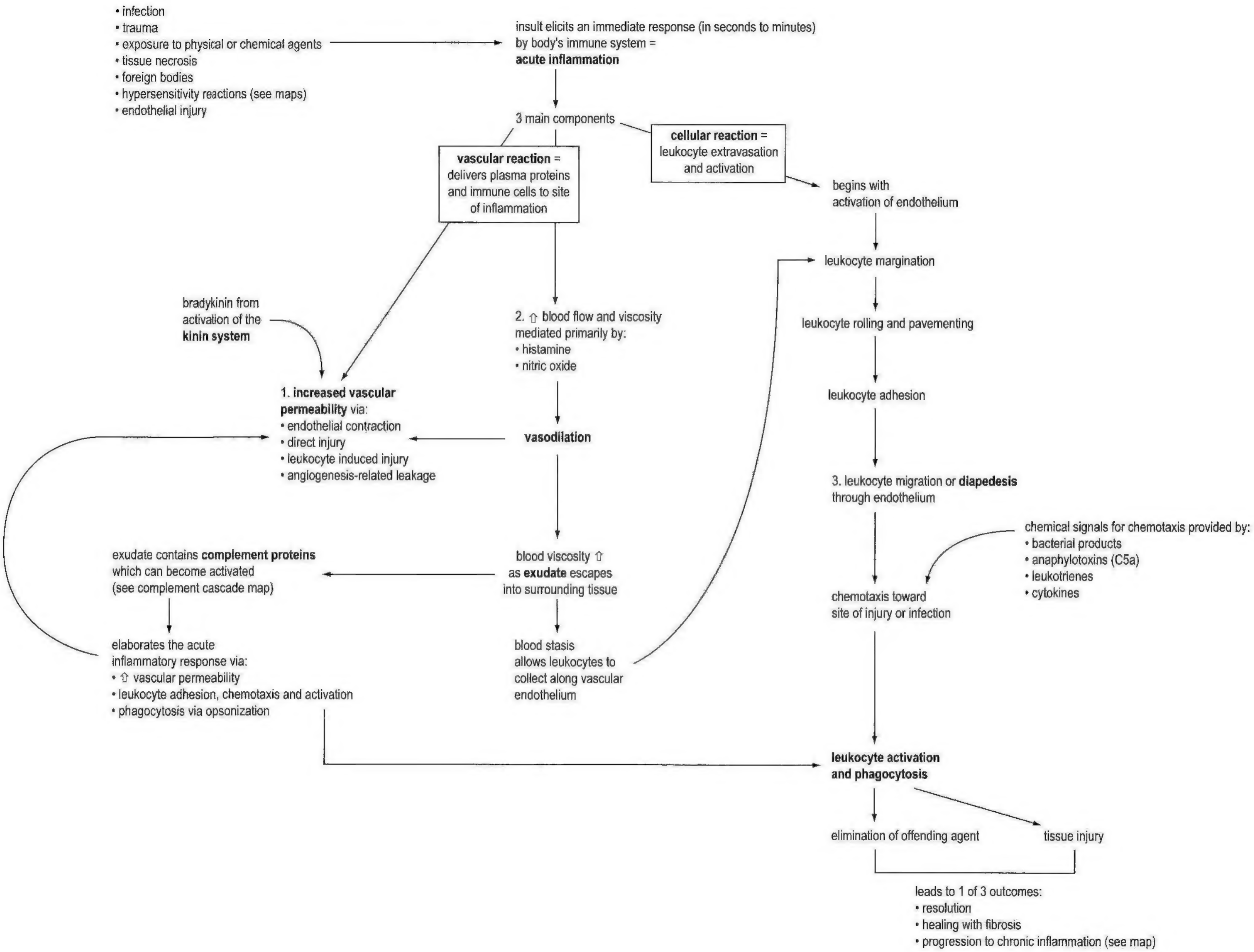
main role of thrombin is to convert **fibrinogen** (factor I) to **fibrin**

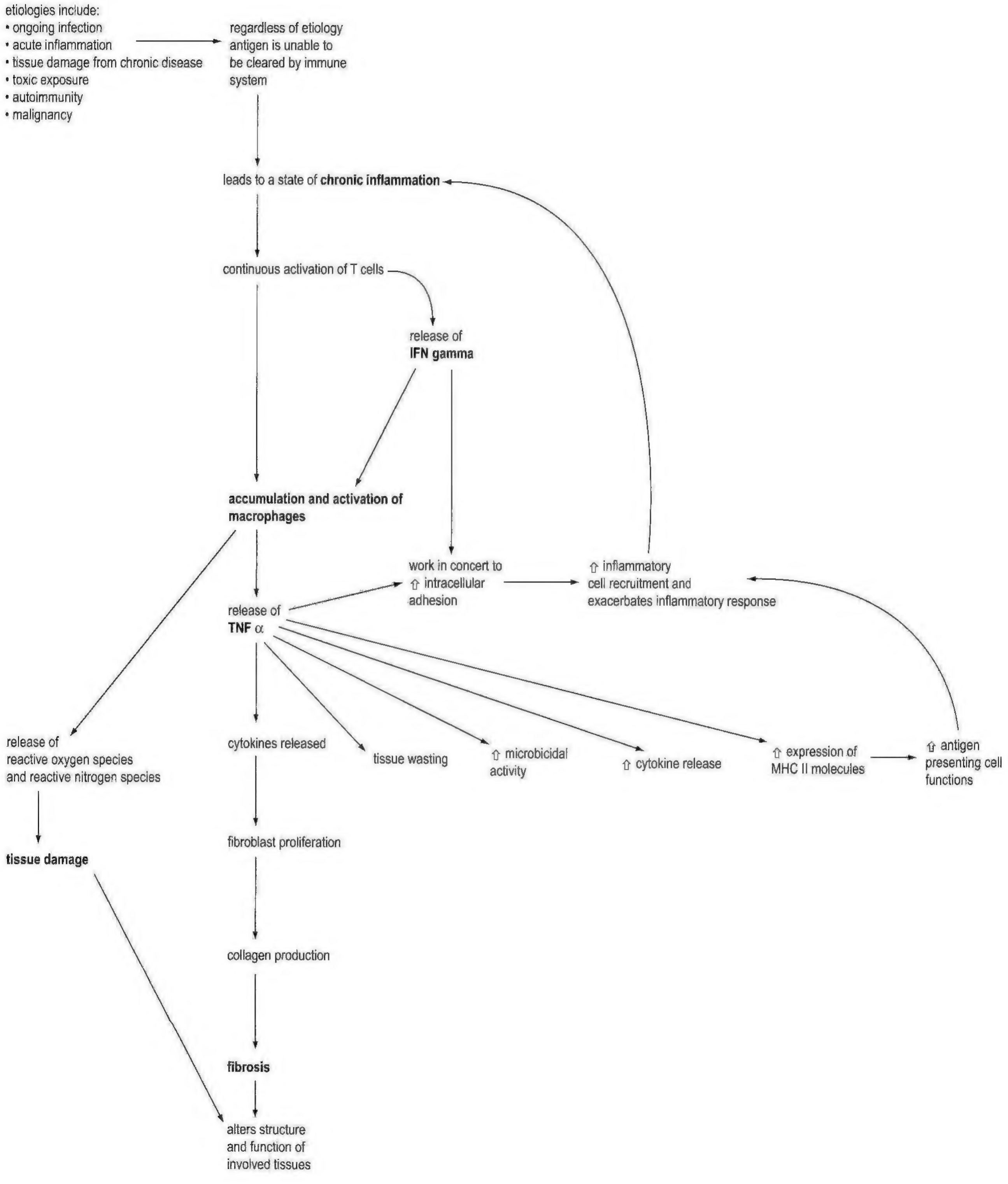
fibrin is cross-linked by **factor XIIIa**

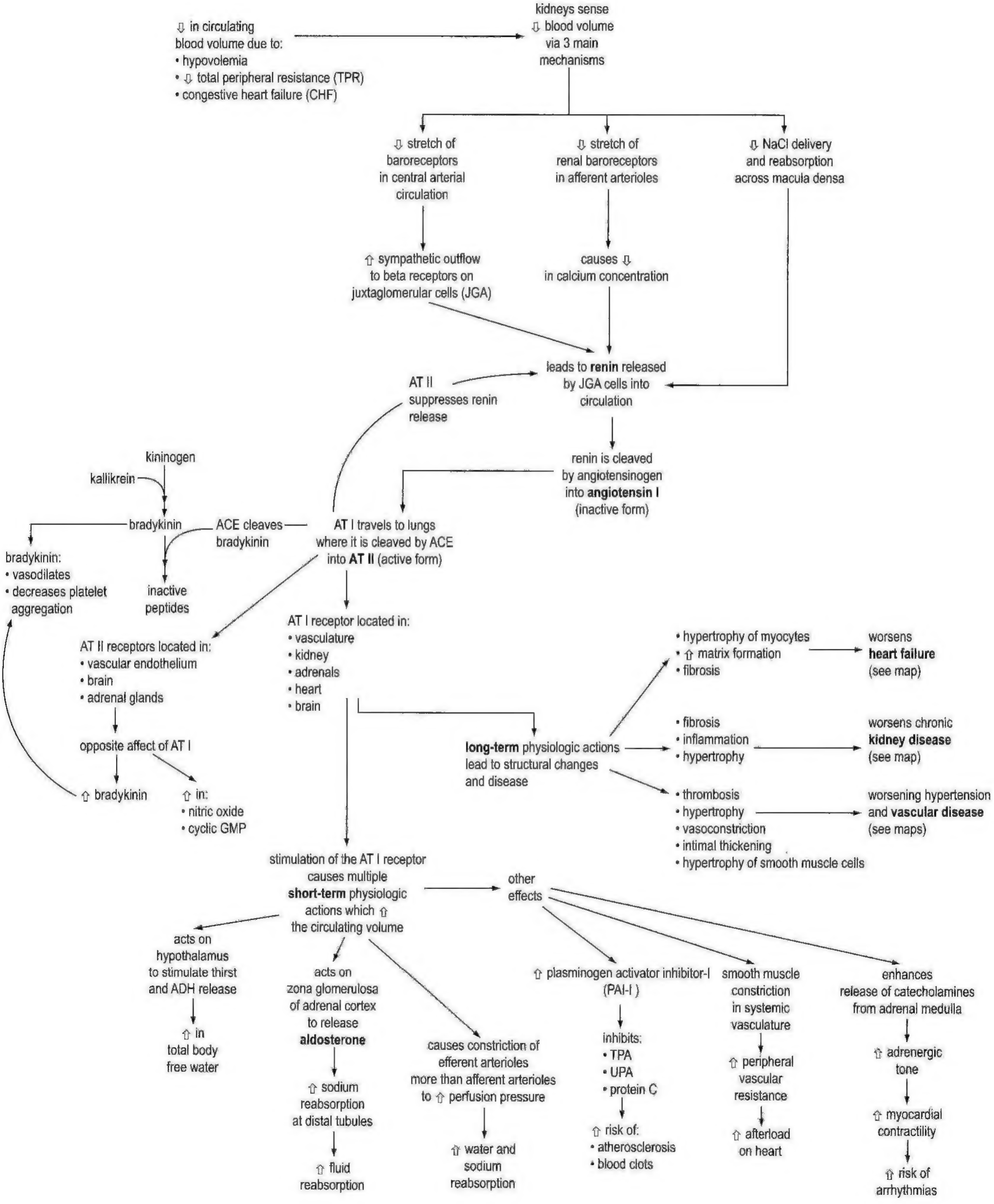
permanent clot is formed as fibrin combines with **platelet aggregates**

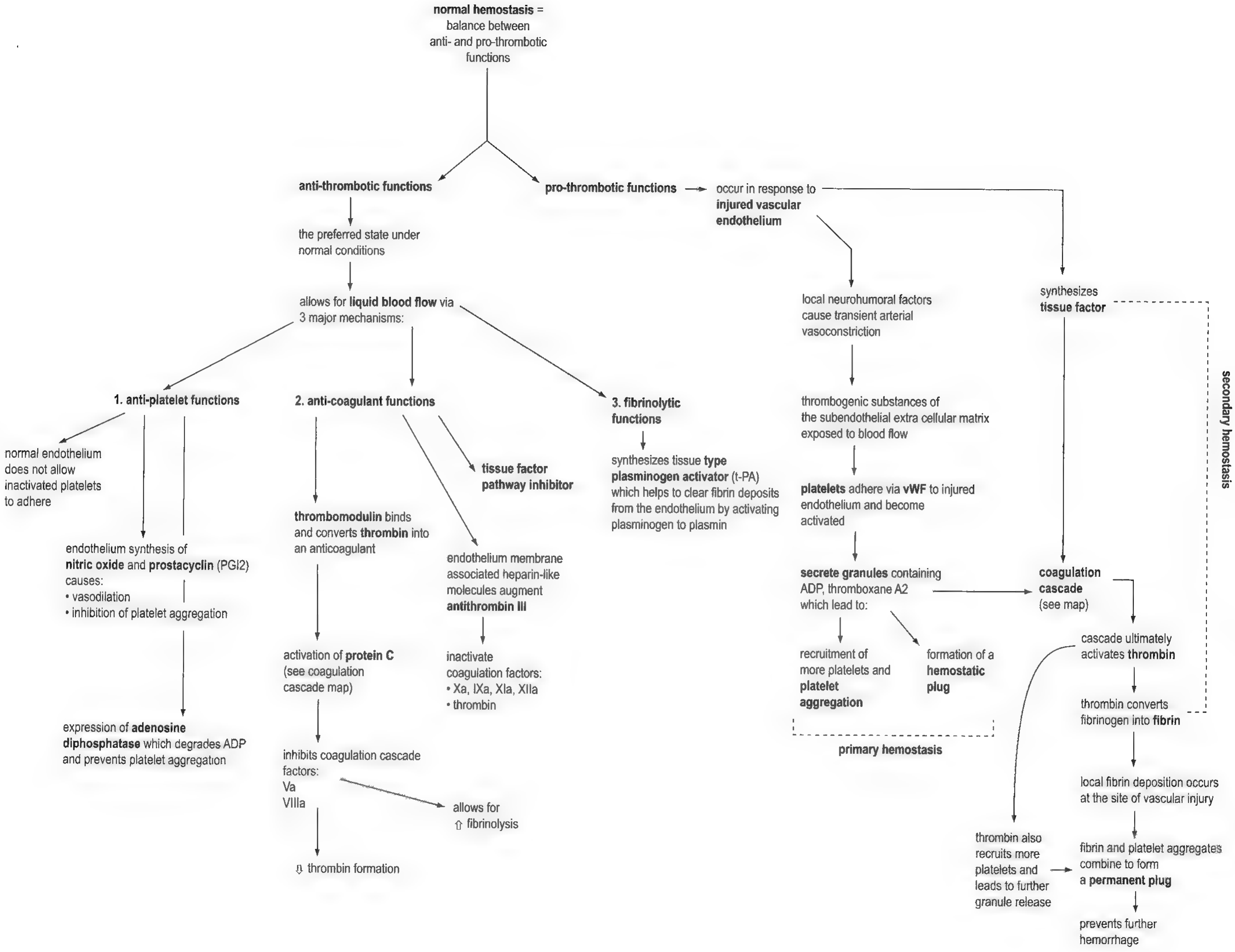

first exposure to antigen:
• intracellular
• tumor cell
antigen is delivered to secondary lymphoid tissue
activation phase
antigen presenting cell (APC) displays antigen to **naive T cell** via peptide: class I MHC complex
APC also provides T cell with costimulatory signal (B7 molecule)
lack of costimulatory signal causes **anergy** = T cell unable to respond to antigenic stimulation
binds CD28 receptor on T cell
T cell activation or priming
activated T cell undergoes proliferation, differentiation and **clonal expansion** into antigen specific **effector T cells**
activated T cell secretes **IL 2**
promotes further clonal expansion
helps T cell develop effector functions
CD4 helper T cell
effector phase
CD4 T cell further differentiates into 1 of 2 T-helper cell types
cytotoxic CD8 T cell
travels to site of infection
effector functions include
releases **cytokines** such as:
• IFN gamma
• TNF alpha
releases **cytotoxins** such as:
• perforin
• granzymes
IFN gamma enhances activation of macrophages
these 2 pathways are not always mutually exclusive
kill infected target cell by inducing **apoptosis** in 2 ways:
• cytotoxins
• Fas ligand
if secretes a Th2 cell cytokine profile
if secretes a **Th1 cell cytokine profile**
humoral immune response (see map)
cell mediated inflammatory response
activates macrophages via IFN gamma and CD40 ligand
activates endothelium
proliferation of effector T cell population
⇧ expression of MHC class II molecules and B7 costimulatory signals
macrophages phagocytize bacteria or other offending agent
bystander tissue damage
enables inflammatory response to progress (see acute inflammation map)
amplifies inflammatory response
⇧ antigen presentation to T cells
granuloma forms if macrophages are unable to eliminate antigen (see sarcoid and TB maps)
amplifies immune response

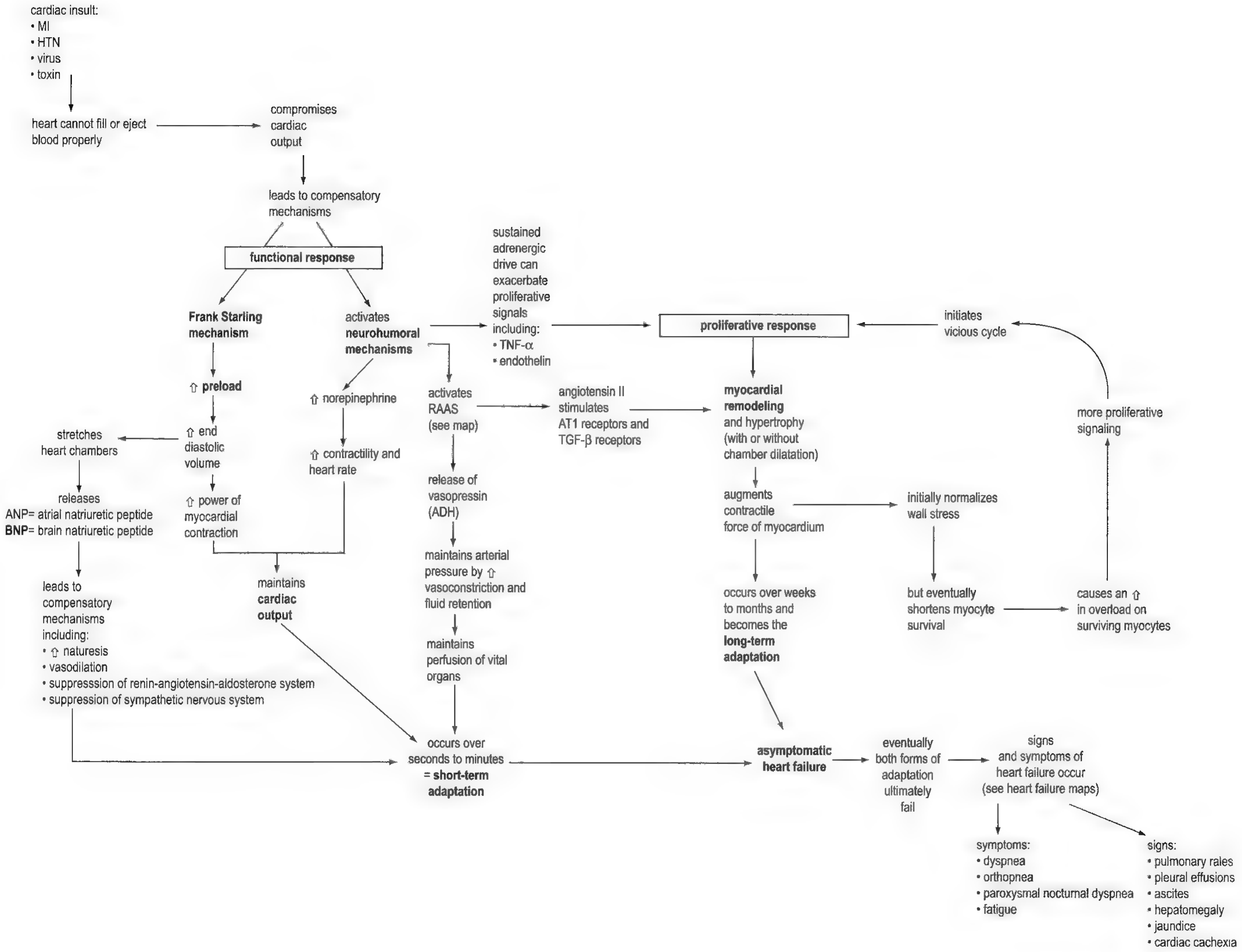

first exposure to antigen elicits a **primary adaptive immune response**
2 types of antigen seen by B cells during this response
majority of antigens seen by B cells
thymus independent antigens = B cells **don't** need T cell help to activate
thymus dependent antigens = B cells **do** need T cell help to activate
antigen is delivered to lymph node where it is recognized by both B and T cells
humoral immune response cannot begin without B and T cell cooperation
antigen is processed and presented by APC to naive T cells
antigen is bound by surface IgM on naive **B cell**
antigen is internalized, processed and then presented on a MHC class II molecule to Th2 cell
CD4 helper T cells activated
secretes **Th2** cell cytokine profile: • especially IL 4
secretes Th1 cell cytokine profile
cell-mediated inflammatory response (see map)
linked recognition = activation of B cell requires antigen recognition by both B and T cells
T helper cells produce CD40 ligand
CD40 ligand on T cells binds CD40 receptor on B cell and induces **activation of the B cell**
enables isotype switching and helps the germinal center to survive
B cells form a **primary focus** within the lymph node for clonal expansion (immediate response)
B cells travel to **primary lymphoid follicle**
form a **germinal center** where antigen specific B cells called **centroblasts** proliferate
somatic hypermutation = creates a set of B cells with varying ability to bind the same antigen
B cells which have a lesser ability to bind the antigen die off within the germinal center = **negative selection**
results in a small number of these B cells that have a greater ability to bind the antigen = **affinity maturation**
B cells with the highest affinity for the antigen are selected and give rise to both
occurs at the same time as **isotype switching**
different classes of antibodies specific for the same antigen are produced
memory B cells
provides body with ability to fight future exposure to same antigen = **secondary adaptive immune response**
plasma cells
secretes antibodies into serum
allow for **2 main effector functions** of B cells to be carried out against antigen
neutralize pathogens = binding and preventing pathogens from entering cells
enable **phagocytosis** via 2 ways:
• opsonization
• complement activation (see map)

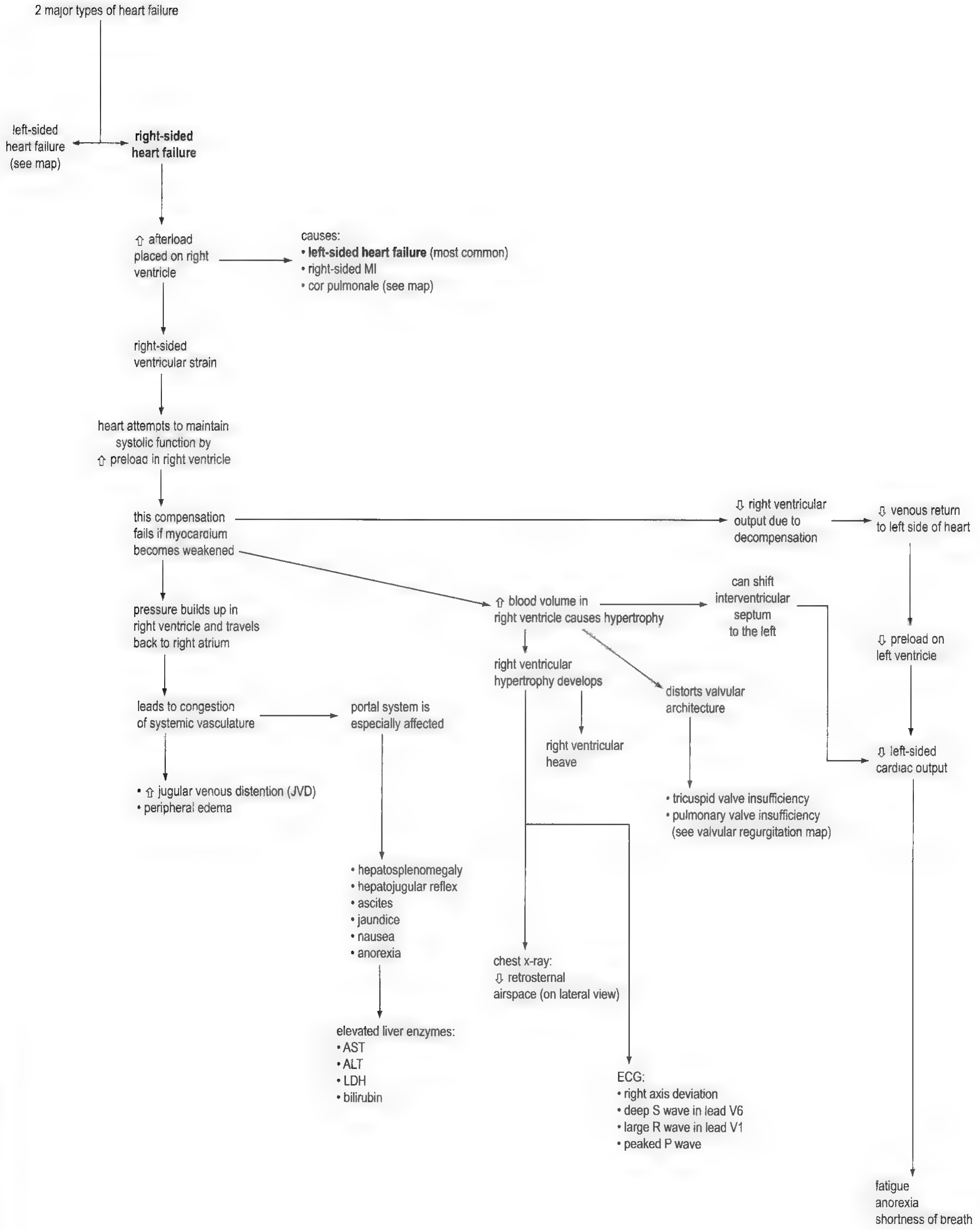

• infection
• trauma
• exposure to physical or chemical agents
• tissue necrosis
• foreign bodies
• hypersensitivity reactions (see maps)
• endothelial injury
insult elicits an immediate response (in seconds to minutes) by body's immune system = **acute inflammation**
3 main components
vascular reaction = delivers plasma proteins and immune cells to site of inflammation
cellular reaction = leukocyte extravasation and activation
begins with activation of endothelium
leukocyte margination
leukocyte rolling and pavementing
leukocyte adhesion
3. leukocyte migration or **diapedesis** through endothelium
chemical signals for chemotaxis provided by:
• bacterial products
• anaphylotoxins (C5a)
• leukotrienes
• cytokines
chemotaxis toward site of injury or infection
leukocyte activation and phagocytosis
elimination of offending agent
tissue injury
leads to 1 of 3 outcomes:
• resolution
• healing with fibrosis
• progression to chronic inflammation (see map)
bradykinin from activation of the **kinin system**
1. **increased vascular permeability** via:
• endothelial contraction
• direct injury
• leukocyte induced injury
• angiogenesis-related leakage
2. ⇧ blood flow and viscosity mediated primarily by:
• histamine
• nitric oxide
vasodilation
blood viscosity ⇧ as **exudate** escapes into surrounding tissue
blood stasis allows leukocytes to collect along vascular endothelium
exudate contains **complement proteins** which can become activated (see complement cascade map)
elaborates the acute inflammatory response via:
• ⇧ vascular permeability
• leukocyte adhesion, chemotaxis and activation
• phagocytosis via opsonization

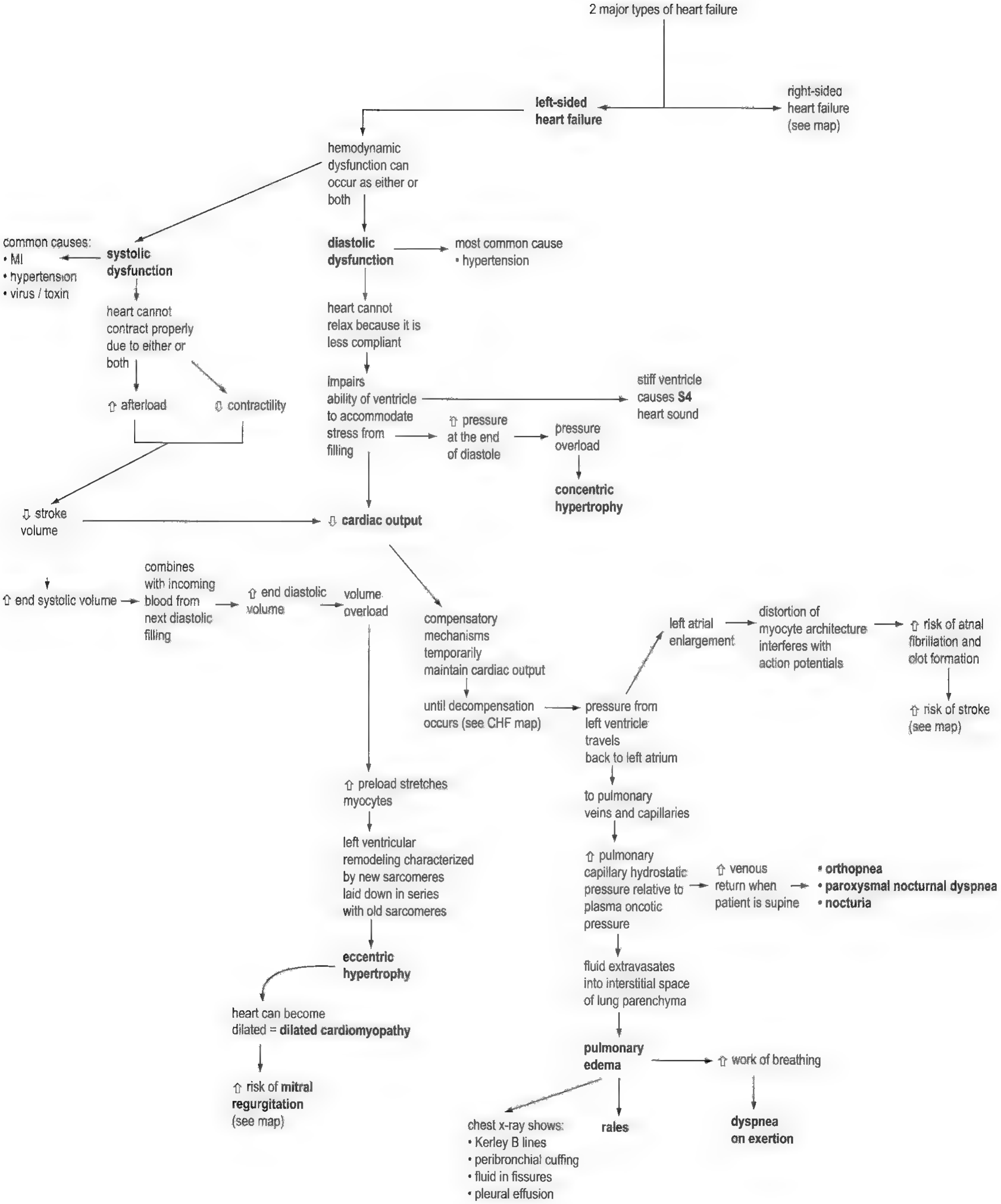

etiologies include:
• ongoing infection
• acute inflammation
• tissue damage from chronic disease
• toxic exposure
• autoimmunity
• malignancy
regardless of etiology antigen is unable to be cleared by immune system
leads to a state of **chronic inflammation**
continuous activation of T cells
release of **IFN gamma**
accumulation and activation of macrophages
work in concert to ⇧ intracellular adhesion
⇧ inflammatory cell recruitment and exacerbates inflammatory response
release of **TNF** α
release of reactive oxygen species and reactive nitrogen species
cytokines released
tissue wasting
⇧ microbicidal activity
⇧ cytokine release
⇧ expression of MHC II molecules
⇧ antigen presenting cell functions
tissue damage
fibroblast proliferation
collagen production
fibrosis
alters structure and function of involved tissues

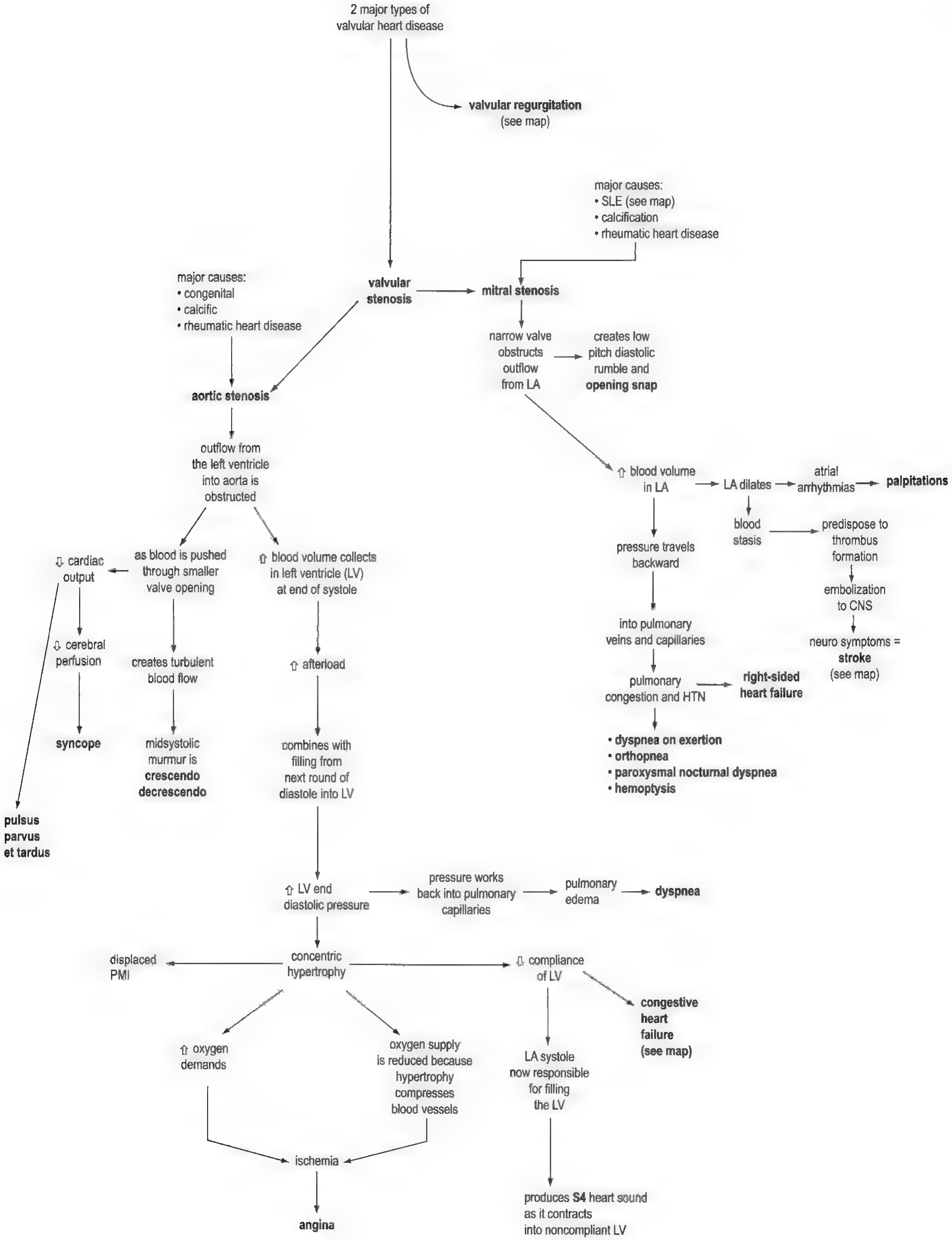

⇩ in circulating blood volume due to: • hypovolemia • ⇩ total peripheral resistance (TPR) • congestive heart failure (CHF)
kidneys sense ⇩ blood volume via 3 main mechanisms
⇩ stretch of baroreceptors in central arterial circulation
⇩ stretch of renal baroreceptors in afferent arterioles
⇩ NaCl delivery and reabsorption across macula densa
⇧ sympathetic outflow to beta receptors on juxtaglomerular cells (JGA)
causes ⇩ in calcium concentration
leads to renin released by JGA cells into circulation
AT II suppresses renin release
renin is cleaved by angiotensinogen into angiotensin I (inactive form)
kininogen
kallikrein
bradykinin
ACE cleaves bradykinin
AT I travels to lungs where it is cleaved by ACE into AT II (active form)
bradykinin: • vasodilates • decreases platelet aggregation
inactive peptides
AT II receptors located in: • vascular endothelium • brain • adrenal glands
opposite affect of AT I
⇧ bradykinin
⇧ in: • nitric oxide • cyclic GMP
AT I receptor located in: • vasculature • kidney • adrenals • heart • brain
long-term physiologic actions lead to structural changes and disease
• hypertrophy of myocytes • ⇧ matrix formation • fibrosis
worsens heart failure (see map)
• fibrosis • inflammation • hypertrophy
worsens chronic kidney disease (see map)
• thrombosis • hypertrophy • vasoconstriction • intimal thickening • hypertrophy of smooth muscle cells
worsening hypertension and vascular disease (see maps)
stimulation of the AT I receptor causes multiple short-term physiologic actions which ⇧ the circulating volume
other effects
acts on hypothalamus to stimulate thirst and ADH release
⇧ in total body free water
acts on zona glomerulosa of adrenal cortex to release aldosterone
⇧ sodium reabsorption at distal tubules
⇧ fluid reabsorption
causes constriction of efferent arterioles more than afferent arterioles to ⇧ perfusion pressure
⇧ water and sodium reabsorption
⇧ plasminogen activator inhibitor-I (PAI-I)
inhibits: • TPA • UPA • protein C
⇧ risk of: • atherosclerosis • blood clots
smooth muscle constriction in systemic vasculature
⇧ peripheral vascular resistance
⇧ afterload on heart
enhances release of catecholamines from adrenal medulla
⇧ adrenergic tone
⇧ myocardial contractility
⇧ risk of arrhythmias

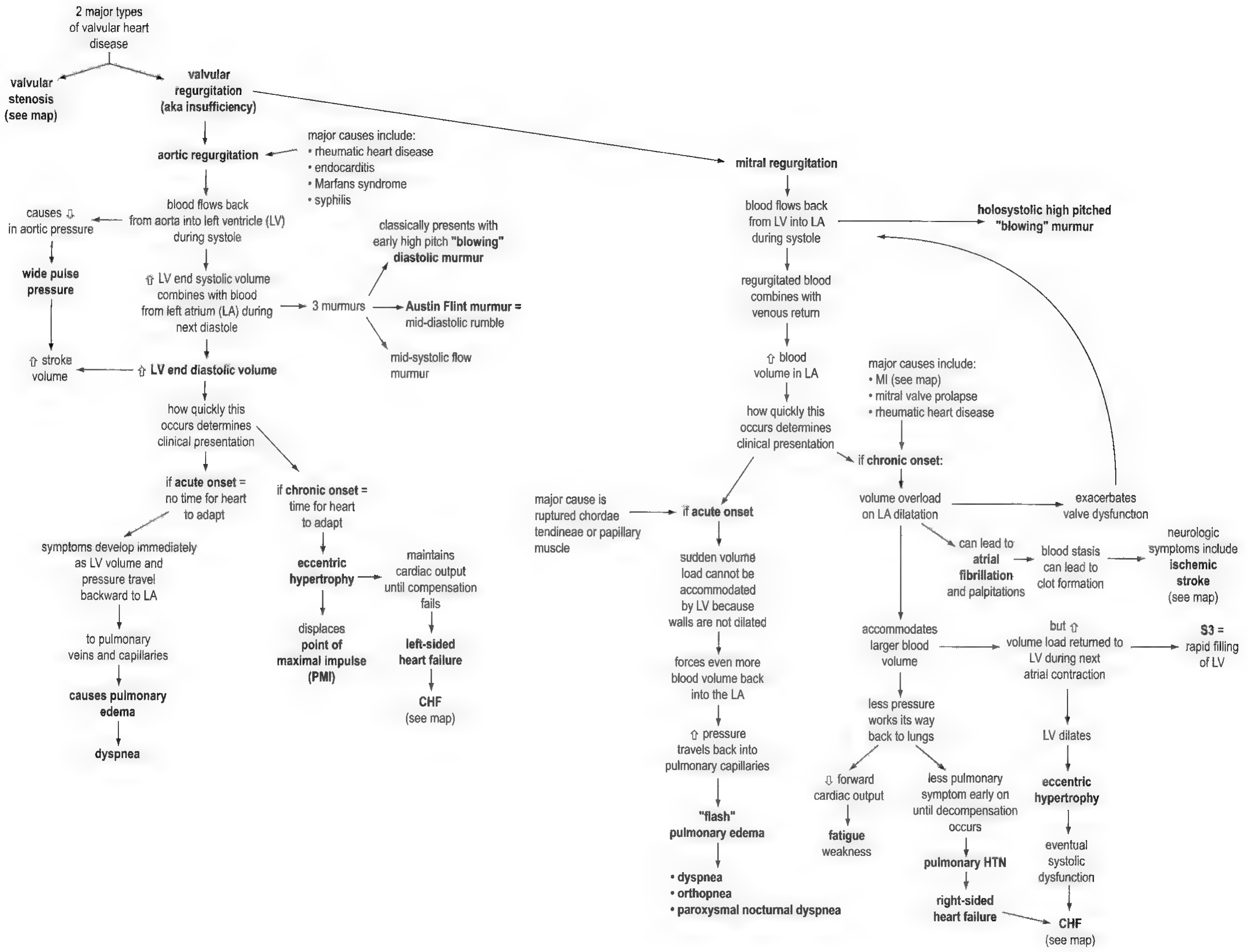

normal hemostasis = balance between anti- and pro-thrombotic functions
anti-thrombotic functions
pro-thrombotic functions
occur in response to injured vascular endothelium
the preferred state under normal conditions
allows for liquid blood flow via 3 major mechanisms:
1. anti-platelet functions
2. anti-coagulant functions
3. fibrinolytic functions
normal endothelium does not allow inactivated platelets to adhere
endothelium synthesis of nitric oxide and prostacyclin (PGI2) causes:
• vasodilation
• inhibition of platelet aggregation
expression of adenosine diphosphatase which degrades ADP and prevents platelet aggregation
thrombomodulin binds and converts thrombin into an anticoagulant
tissue factor pathway inhibitor
endothelium membrane associated heparin-like molecules augment antithrombin III
inactivate coagulation factors:
• Xa, IXa, XIa, XIIa
• thrombin
activation of protein C (see coagulation cascade map)
inhibits coagulation cascade factors:
Va
VIIIa
allows for ⇧ fibrinolysis
⇩ thrombin formation
synthesizes tissue type plasminogen activator (t-PA) which helps to clear fibrin deposits from the endothelium by activating plasminogen to plasmin
local neurohumoral factors cause transient arterial vasoconstriction
thrombogenic substances of the subendothelial extra cellular matrix exposed to blood flow
platelets adhere via vWF to injured endothelium and become activated
secrete granules containing ADP, thromboxane A2 which lead to:
recruitment of more platelets and platelet aggregation
formation of a hemostatic plug
primary hemostasis
synthesizes tissue factor
secondary hemostasis
coagulation cascade (see map)
cascade ultimately activates thrombin
thrombin converts fibrinogen into fibrin
local fibrin deposition occurs at the site of vascular injury
thrombin also recruits more platelets and leads to further granule release
fibrin and platelet aggregates combine to form a permanent plug
prevents further hemorrhage

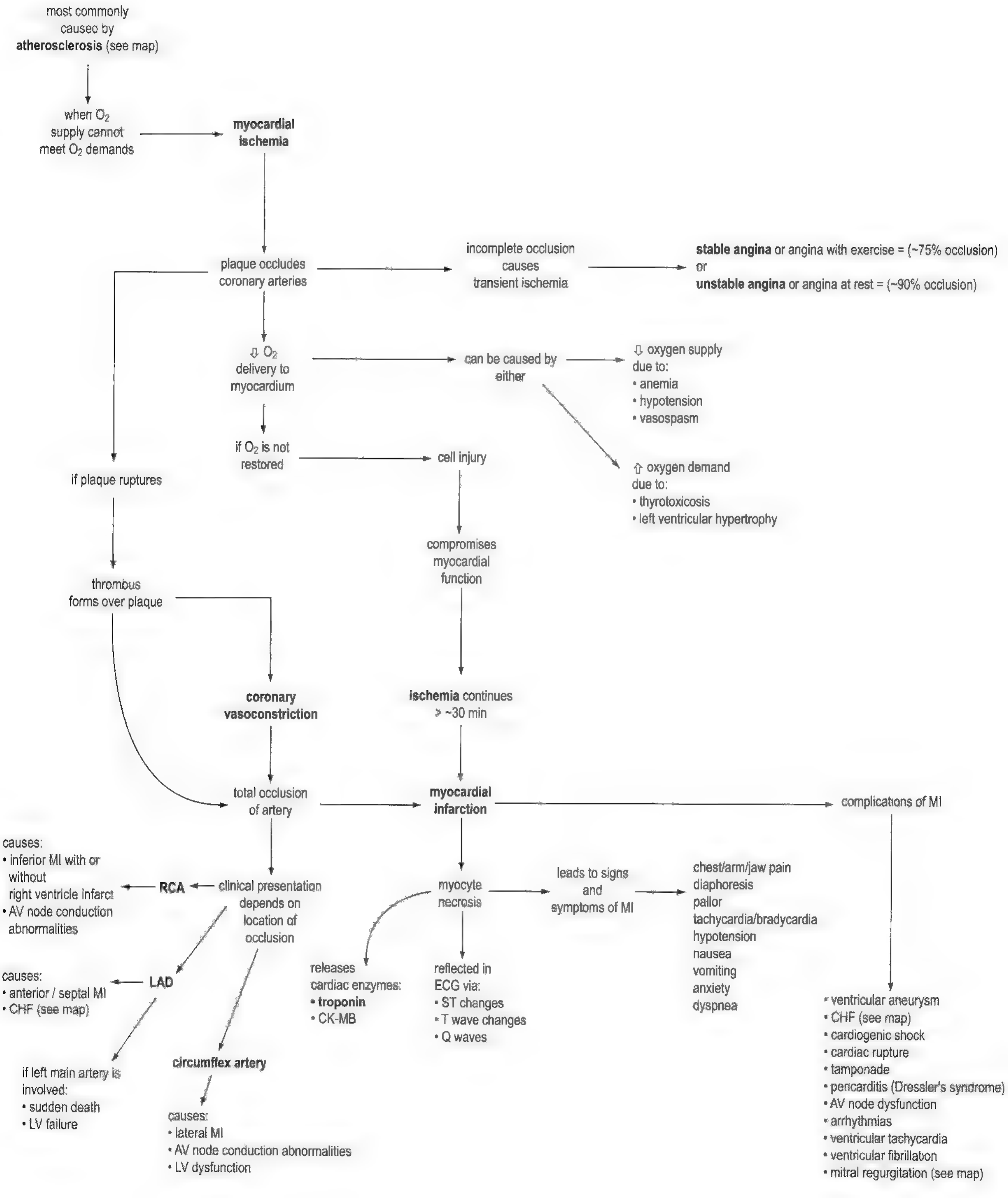

cardiac insult:
• MI
• HTN
• virus
• toxin
heart cannot fill or eject blood properly
compromises cardiac output
leads to compensatory mechanisms
functional response
Frank Starling mechanism
⇧ preload
⇧ end diastolic volume
⇧ power of myocardial contraction
stretches heart chambers
releases
ANP= atrial natriuretic peptide
BNP= brain natriuretic peptide
leads to compensatory mechanisms including:
• ⇧ naturesis
• vasodilation
• suppresssion of renin-angiotensin-aldosterone system
• suppression of sympathetic nervous system
activates neurohumoral mechanisms
⇧ norepinephrine
⇧ contractility and heart rate
maintains cardiac output
activates RAAS (see map)
release of vasopressin (ADH)
maintains arterial pressure by ⇧ vasoconstriction and fluid retention
maintains perfusion of vital organs
occurs over seconds to minutes = short-term adaptation
sustained adrenergic drive can exacerbate proliferative signals including:
• TNF-α
• endothelin
angiotensin II stimulates AT1 receptors and TGF-β receptors
proliferative response
myocardial remodeling and hypertrophy (with or without chamber dilatation)
augments contractile force of myocardium
occurs over weeks to months and becomes the long-term adaptation
initially normalizes wall stress
but eventually shortens myocyte survival
causes an ⇧ in overload on surviving myocytes
more proliferative signaling
initiates vicious cycle
asymptomatic heart failure
eventually both forms of adaptation ultimately fail
signs and symptoms of heart failure occur (see heart failure maps)
symptoms:
• dyspnea
• orthopnea
• paroxysmal nocturnal dyspnea
• fatigue
signs:
• pulmonary rales
• pleural effusions
• ascites
• hepatomegaly
• jaundice
• cardiac cachexia

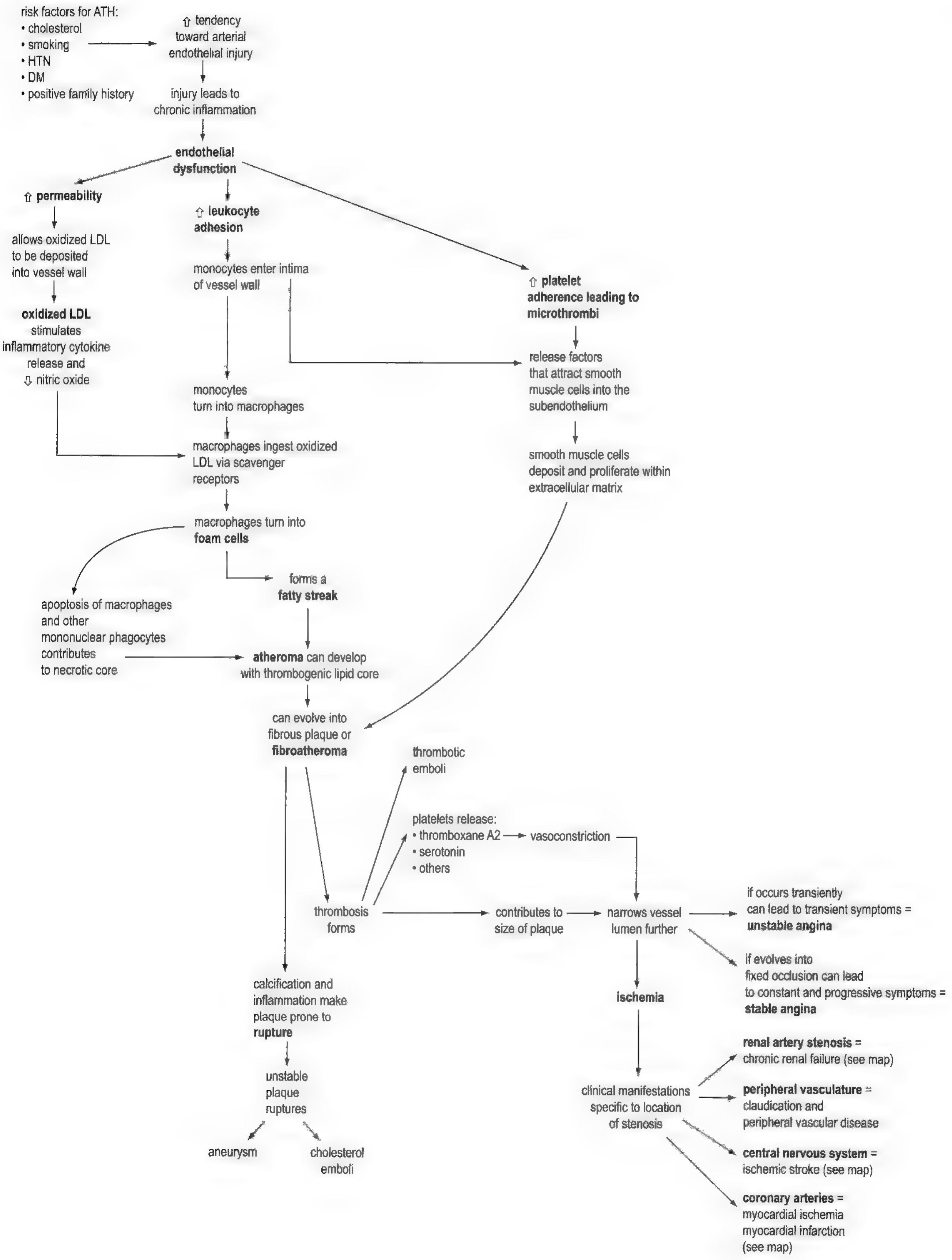

2 major types of heart failure
left-sided heart failure (see map)
right-sided heart failure
⇧ afterload placed on right ventricle
causes:
• **left-sided heart failure** (most common)
• right-sided MI
• cor pulmonale (see map)
right-sided ventricular strain
heart attempts to maintain systolic function by ⇧ preload in right ventricle
this compensation fails if myocardium becomes weakened
⇩ right ventricular output due to decompensation
⇩ venous return to left side of heart
pressure builds up in right ventricle and travels back to right atrium
⇧ blood volume in right ventricle causes hypertrophy
can shift interventricular septum to the left
⇩ preload on left ventricle
right ventricular hypertrophy develops
distorts valvular architecture
leads to congestion of systemic vasculature
portal system is especially affected
right ventricular heave
⇩ left-sided cardiac output
• ⇧ jugular venous distention (JVD)
• peripheral edema
• tricuspid valve insufficiency
• pulmonary valve insufficiency (see valvular regurgitation map)
• hepatosplenomegaly
• hepatojugular reflex
• ascites
• jaundice
• nausea
• anorexia
chest x-ray: ⇩ retrosternal airspace (on lateral view)
elevated liver enzymes:
• AST
• ALT
• LDH
• bilirubin
ECG:
• right axis deviation
• deep S wave in lead V6
• large R wave in lead V1
• peaked P wave
fatigue
anorexia
shortness of breath

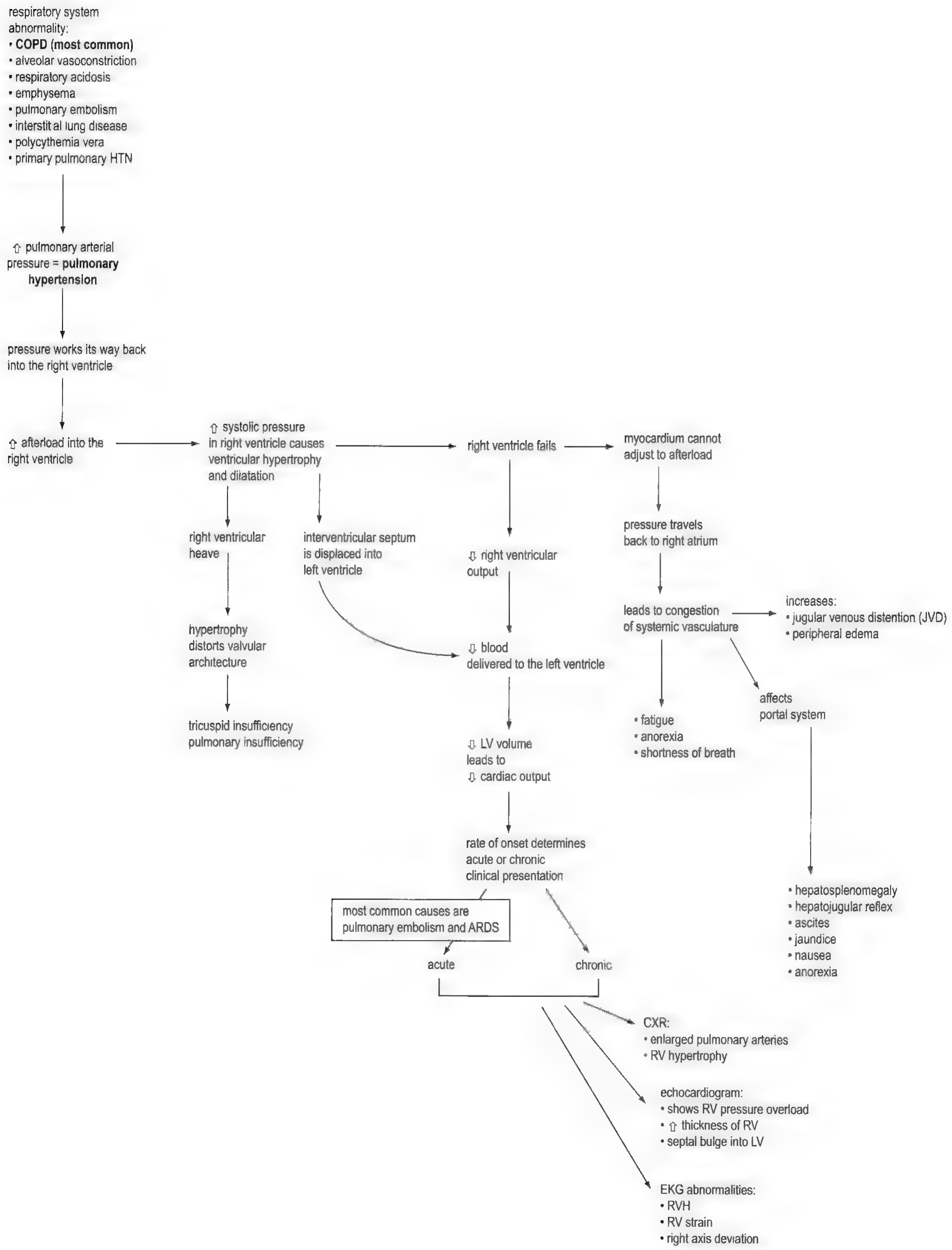

2 major types of heart failure
left-sided heart failure
right-sided heart failure (see map)
hemodynamic dysfunction can occur as either or both
systolic dysfunction
common causes:
• MI
• hypertension
• virus / toxin
diastolic dysfunction
most common cause
• hypertension
heart cannot contract properly due to either or both
⇧ afterload
⇩ contractility
⇩ stroke volume
heart cannot relax because it is less compliant
impairs ability of ventricle to accommodate stress from filling
stiff ventricle causes S4 heart sound
⇧ pressure at the end of diastole
pressure overload
concentric hypertrophy
⇩ cardiac output
⇧ end systolic volume
combines with incoming blood from next diastolic filling
⇧ end diastolic volume
volume overload
compensatory mechanisms temporarily maintain cardiac output
until decompensation occurs (see CHF map)
pressure from left ventricle travels back to left atrium
left atrial enlargement
distortion of myocyte architecture interferes with action potentials
⇧ risk of atrial fibrillation and clot formation
⇧ risk of stroke (see map)
to pulmonary veins and capillaries
⇧ pulmonary capillary hydrostatic pressure relative to plasma oncotic pressure
⇧ venous return when patient is supine
• orthopnea
• paroxysmal nocturnal dyspnea
• nocturia
fluid extravasates into interstitial space of lung parenchyma
pulmonary edema
⇧ work of breathing
dyspnea on exertion
rales
chest x-ray shows:
• Kerley B lines
• peribronchial cuffing
• fluid in fissures
• pleural effusion
⇧ preload stretches myocytes
left ventricular remodeling characterized by new sarcomeres laid down in series with old sarcomeres
eccentric hypertrophy
heart can become dilated = dilated cardiomyopathy
⇧ risk of mitral regurgitation (see map)

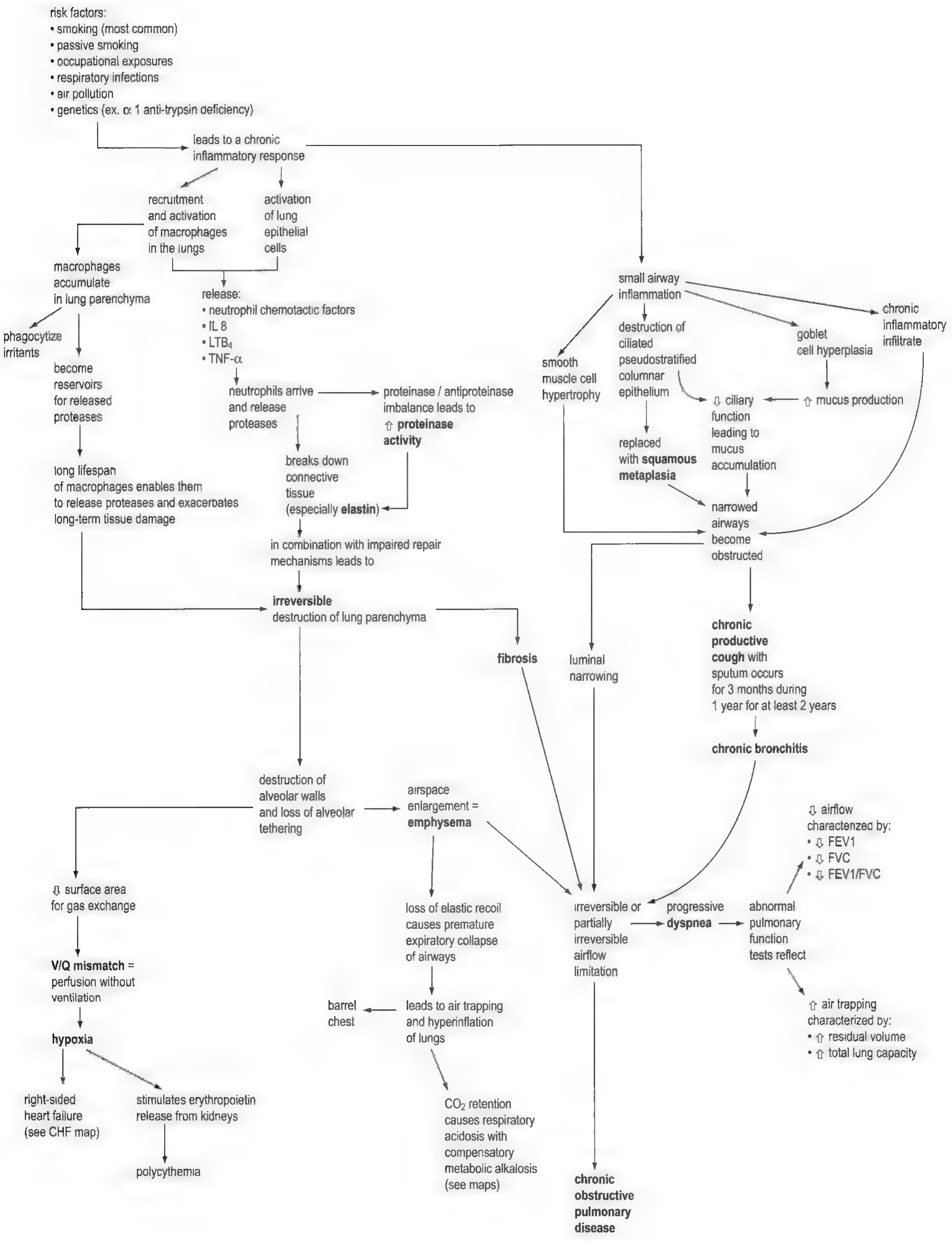

2 major types of valvular heart disease
valvular regurgitation (see map)
valvular stenosis
major causes:
• SLE (see map)
• calcification
• rheumatic heart disease
mitral stenosis
narrow valve obstructs outflow from LA
creates low pitch diastolic rumble and opening snap
⇧ blood volume in LA
LA dilates
atrial arrhythmias
palpitations
blood stasis
predispose to thrombus formation
embolization to CNS
neuro symptoms = stroke (see map)
pressure travels backward
into pulmonary veins and capillaries
pulmonary congestion and HTN
right-sided heart failure
• dyspnea on exertion
• orthopnea
• paroxysmal nocturnal dyspnea
• hemoptysis
major causes:
• congenital
• calcific
• rheumatic heart disease
aortic stenosis
outflow from the left ventricle into aorta is obstructed
as blood is pushed through smaller valve opening
⇩ cardiac output
⇩ cerebral perfusion
syncope
pulsus parvus et tardus
creates turbulent blood flow
midsystolic murmur is crescendo decrescendo
⇧ blood volume collects in left ventricle (LV) at end of systole
⇧ afterload
combines with filling from next round of diastole into LV
⇧ LV end diastolic pressure
pressure works back into pulmonary capillaries
pulmonary edema
dyspnea
concentric hypertrophy
displaced PMI
⇩ compliance of LV
congestive heart failure (see map)
⇧ oxygen demands
oxygen supply is reduced because hypertrophy compresses blood vessels
ischemia
angina
LA systole now responsible for filling the LV
produces S4 heart sound as it contracts into noncompliant LV

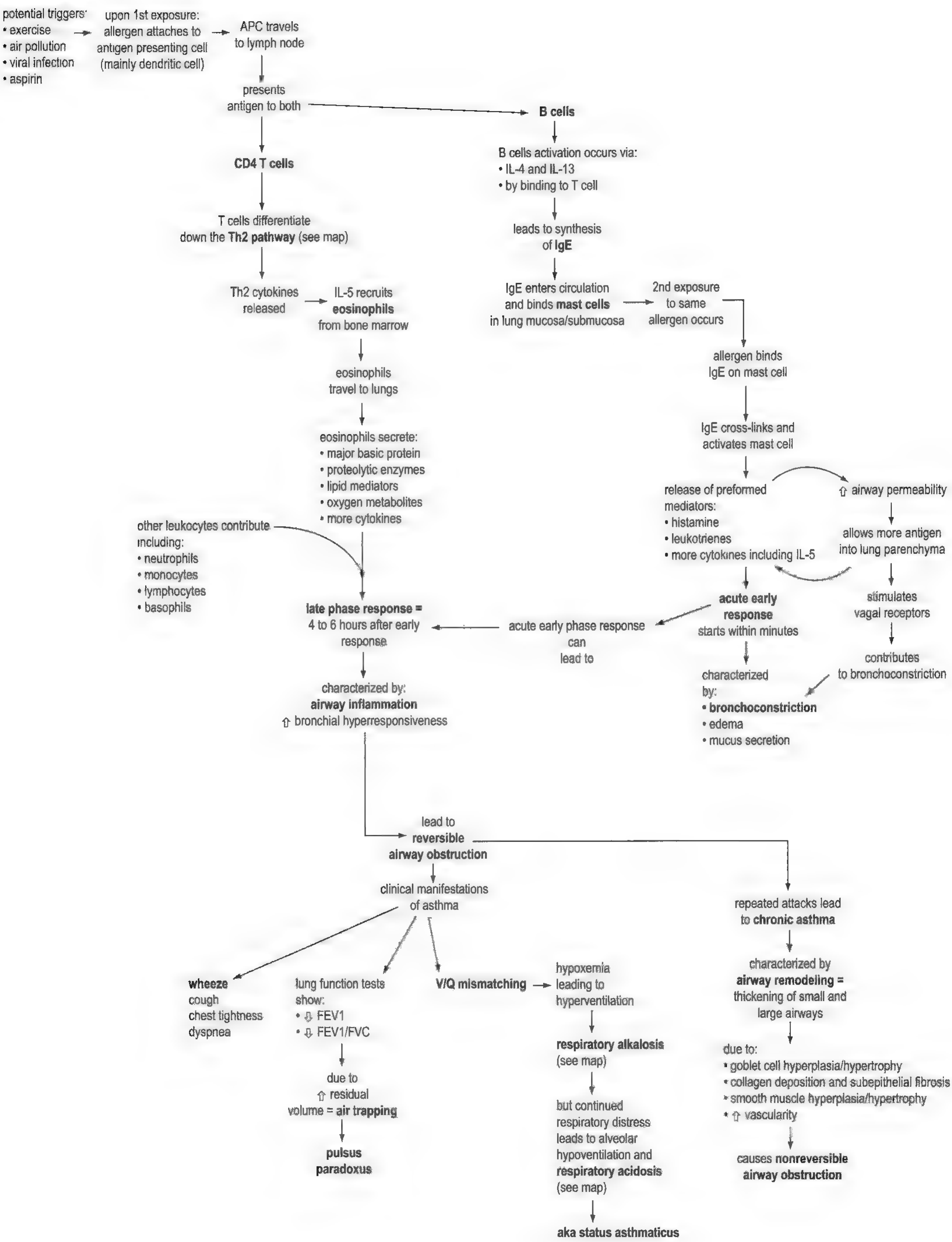

2 major types of valvular heart disease
valvular stenosis (see map)
valvular regurgitation (aka insufficiency)
aortic regurgitation
major causes include:
• rheumatic heart disease
• endocarditis
• Marfans syndrome
• syphilis
blood flows back from aorta into left ventricle (LV) during systole
causes ⇩ in aortic pressure
wide pulse pressure
⇧ stroke volume
⇧ LV end systolic volume combines with blood from left atrium (LA) during next diastole
3 murmurs
classically presents with early high pitch "blowing" diastolic murmur
Austin Flint murmur = mid-diastolic rumble
mid-systolic flow murmur
⇧ LV end diastolic volume
how quickly this occurs determines clinical presentation
if acute onset = no time for heart to adapt
symptoms develop immediately as LV volume and pressure travel backward to LA
to pulmonary veins and capillaries
causes pulmonary edema
dyspnea
if chronic onset = time for heart to adapt
eccentric hypertrophy
displaces point of maximal impulse (PMI)
maintains cardiac output until compensation fails
left-sided heart failure
CHF (see map)
mitral regurgitation
blood flows back from LV into LA during systole
holosystolic high pitched "blowing" murmur
regurgitated blood combines with venous return
⇧ blood volume in LA
how quickly this occurs determines clinical presentation
major cause is ruptured chordae tendineae or papillary muscle
if acute onset
sudden volume load cannot be accommodated by LV because walls are not dilated
forces even more blood volume back into the LA
⇧ pressure travels back into pulmonary capillaries
"flash" pulmonary edema
• dyspnea
• orthopnea
• paroxysmal nocturnal dyspnea
major causes include:
• MI (see map)
• mitral valve prolapse
• rheumatic heart disease
if chronic onset:
volume overload on LA dilatation
exacerbates valve dysfunction
can lead to atrial fibrillation and palpitations
blood stasis can lead to clot formation
neurologic symptoms include ischemic stroke (see map)
accommodates larger blood volume
but ⇧ volume load returned to LV during next atrial contraction
S3 = rapid filling of LV
less pressure works its way back to lungs
⇩ forward cardiac output
fatigue weakness
less pulmonary symptom early on until decompensation occurs
pulmonary HTN
right-sided heart failure
LV dilates
eccentric hypertrophy
eventual systolic dysfunction
CHF (see map)


most commonly caused by **atherosclerosis** (see map)
when O_2 supply cannot meet O_2 demands
myocardial ischemia
plaque occludes coronary arteries
incomplete occlusion causes transient ischemia
stable angina or angina with exercise = (~75% occlusion)
or
unstable angina or angina at rest = (~90% occlusion)
⇩ O_2 delivery to myocardium
can be caused by either
⇩ oxygen supply due to:
• anemia
• hypotension
• vasospasm
⇧ oxygen demand due to:
• thyrotoxicosis
• left ventricular hypertrophy
if O_2 is not restored
cell injury
compromises myocardial function
ischemia continues > ~30 min
if plaque ruptures
thrombus forms over plaque
coronary vasoconstriction
total occlusion of artery
myocardial infarction
complications of MI
• ventricular aneurysm
• CHF (see map)
• cardiogenic shock
• cardiac rupture
• tamponade
• pericarditis (Dressler's syndrome)
• AV node dysfunction
• arrhythmias
• ventricular tachycardia
• ventricular fibrillation
• mitral regurgitation (see map)
clinical presentation depends on location of occlusion
RCA
causes:
• inferior MI with or without right ventricle infarct
• AV node conduction abnormalities
LAD
causes:
• anterior / septal MI
• CHF (see map)
if left main artery is involved:
• sudden death
• LV failure
circumflex artery
causes:
• lateral MI
• AV node conduction abnormalities
• LV dysfunction
myocyte necrosis
releases cardiac enzymes:
• **troponin**
• CK-MB
reflected in ECG via:
• ST changes
• T wave changes
• Q waves
leads to signs and symptoms of MI
chest/arm/jaw pain
diaphoresis
pallor
tachycardia/bradycardia
hypotension
nausea
vomiting
anxiety
dyspnea


risk factors for ATH:
• cholesterol
• smoking
• HTN
• DM
• positive family history
⇧ tendency toward arterial endothelial injury
injury leads to chronic inflammation
endothelial dysfunction
⇧ permeability
allows oxidized LDL to be deposited into vessel wall
oxidized LDL stimulates inflammatory cytokine release and ⇩ nitric oxide
⇧ leukocyte adhesion
monocytes enter intima of vessel wall
monocytes turn into macrophages
macrophages ingest oxidized LDL via scavenger receptors
macrophages turn into foam cells
⇧ platelet adherence leading to microthrombi
release factors that attract smooth muscle cells into the subendothelium
smooth muscle cells deposit and proliferate within extracellular matrix
apoptosis of macrophages and other mononuclear phagocytes contributes to necrotic core
forms a fatty streak
atheroma can develop with thrombogenic lipid core
can evolve into fibrous plaque or fibroatheroma
thrombotic emboli
platelets release:
• thromboxane A2
• serotonin
• others
vasoconstriction
thrombosis forms
contributes to size of plaque
narrows vessel lumen further
if occurs transiently can lead to transient symptoms = unstable angina
if evolves into fixed occlusion can lead to constant and progressive symptoms = stable angina
ischemia
clinical manifestations specific to location of stenosis
renal artery stenosis = chronic renal failure (see map)
peripheral vasculature = claudication and peripheral vascular disease
central nervous system = ischemic stroke (see map)
coronary arteries = myocardial ischemia myocardial infarction (see map)
calcification and inflammation make plaque prone to rupture
unstable plaque ruptures
aneurysm
cholesterol emboli


respiratory system abnormality:
• COPD (most common)
• alveolar vasoconstriction
• respiratory acidosis
• emphysema
• pulmonary embolism
• interstitial lung disease
• polycythemia vera
• primary pulmonary HTN
⇧ pulmonary arterial pressure = pulmonary hypertension
pressure works its way back into the right ventricle
⇧ afterload into the right ventricle
⇧ systolic pressure in right ventricle causes ventricular hypertrophy and dilatation
right ventricular heave
hypertrophy distorts valvular architecture
tricuspid insufficiency pulmonary insufficiency
interventricular septum is displaced into left ventricle
right ventricle fails
⇩ right ventricular output
⇩ blood delivered to the left ventricle
⇩ LV volume leads to ⇩ cardiac output
rate of onset determines acute or chronic clinical presentation
most common causes are pulmonary embolism and ARDS
acute
chronic
CXR:
• enlarged pulmonary arteries
• RV hypertrophy
echocardiogram:
• shows RV pressure overload
• ⇧ thickness of RV
• septal bulge into LV
EKG abnormalities:
• RVH
• RV strain
• right axis deviation
myocardium cannot adjust to afterload
pressure travels back to right atrium
leads to congestion of systemic vasculature
increases:
• jugular venous distention (JVD)
• peripheral edema
• fatigue
• anorexia
• shortness of breath
affects portal system
• hepatosplenomegaly
• hepatojugular reflex
• ascites
• jaundice
• nausea
• anorexia


risk factors:
• smoking (most common)
• passive smoking
• occupational exposures
• respiratory infections
• air pollution
• genetics (ex. α 1 anti-trypsin deficiency)
leads to a chronic inflammatory response
recruitment and activation of macrophages in the lungs
activation of lung epithelial cells
macrophages accumulate in lung parenchyma
phagocytize irritants
become reservoirs for released proteases
long lifespan of macrophages enables them to release proteases and exacerbates long-term tissue damage
release:
• neutrophil chemotactic factors
• IL 8
• LTB$_4$
• TNF-α
neutrophils arrive and release proteases
proteinase / antiproteinase imbalance leads to ⇧ proteinase activity
breaks down connective tissue (especially elastin)
in combination with impaired repair mechanisms leads to
irreversible destruction of lung parenchyma
fibrosis
small airway inflammation
smooth muscle cell hypertrophy
destruction of ciliated pseudostratified columnar epithelium
goblet cell hyperplasia
chronic inflammatory infiltrate
⇩ ciliary function leading to mucus accumulation
⇧ mucus production
replaced with squamous metaplasia
narrowed airways become obstructed
luminal narrowing
chronic productive cough with sputum occurs for 3 months during 1 year for at least 2 years
chronic bronchitis
destruction of alveolar walls and loss of alveolar tethering
airspace enlargement = emphysema
⇩ surface area for gas exchange
V/Q mismatch = perfusion without ventilation
hypoxia
right-sided heart failure (see CHF map)
stimulates erythropoietin release from kidneys
polycythemia
loss of elastic recoil causes premature expiratory collapse of airways
leads to air trapping and hyperinflation of lungs
barrel chest
CO$_2$ retention causes respiratory acidosis with compensatory metabolic alkalosis (see maps)
irreversible or partially irreversible airflow limitation
progressive dyspnea
abnormal pulmonary function tests reflect
⇩ airflow characterized by:
• ⇩ FEV1
• ⇩ FVC
• ⇩ FEV1/FVC
⇧ air trapping characterized by:
• ⇧ residual volume
• ⇧ total lung capacity
chronic obstructive pulmonary disease



potential triggers:
- exercise
- air pollution
- viral infection
- aspirin

upon 1st exposure: allergen attaches to antigen presenting cell (mainly dendritic cell)

APC travels to lymph node

presents antigen to both

CD4 T cells

T cells differentiate down the **Th2 pathway** (see map)

Th2 cytokines released

IL-5 recruits **eosinophils** from bone marrow

eosinophils travel to lungs

eosinophils secrete:
- major basic protein
- proteolytic enzymes
- lipid mediators
- oxygen metabolites
- more cytokines

other leukocytes contribute including:
- neutrophils
- monocytes
- lymphocytes
- basophils

B cells

B cells activation occurs via:
- IL-4 and IL-13
- by binding to T cell

leads to synthesis of **IgE**

IgE enters circulation and binds **mast cells** in lung mucosa/submucosa

2nd exposure to same allergen occurs

allergen binds IgE on mast cell

IgE cross-links and activates mast cell

release of preformed mediators:
- histamine
- leukotrienes
- more cytokines including IL-5

⇧ airway permeability

allows more antigen into lung parenchyma

stimulates vagal receptors

contributes to bronchoconstriction

acute early response starts within minutes

characterized by:
- **bronchoconstriction**
- edema
- mucus secretion

acute early phase response can lead to

late phase response = 4 to 6 hours after early response

characterized by:
airway inflammation
⇧ bronchial hyperresponsiveness

lead to **reversible airway obstruction**

clinical manifestations of asthma

wheeze
cough
chest tightness
dyspnea

lung function tests show:
- ⇩ FEV1
- ⇩ FEV1/FVC

due to ⇧ residual volume = **air trapping**

pulsus paradoxus

V/Q mismatching

hypoxemia leading to hyperventilation

respiratory alkalosis (see map)

but continued respiratory distress leads to alveolar hypoventilation and **respiratory acidosis** (see map)

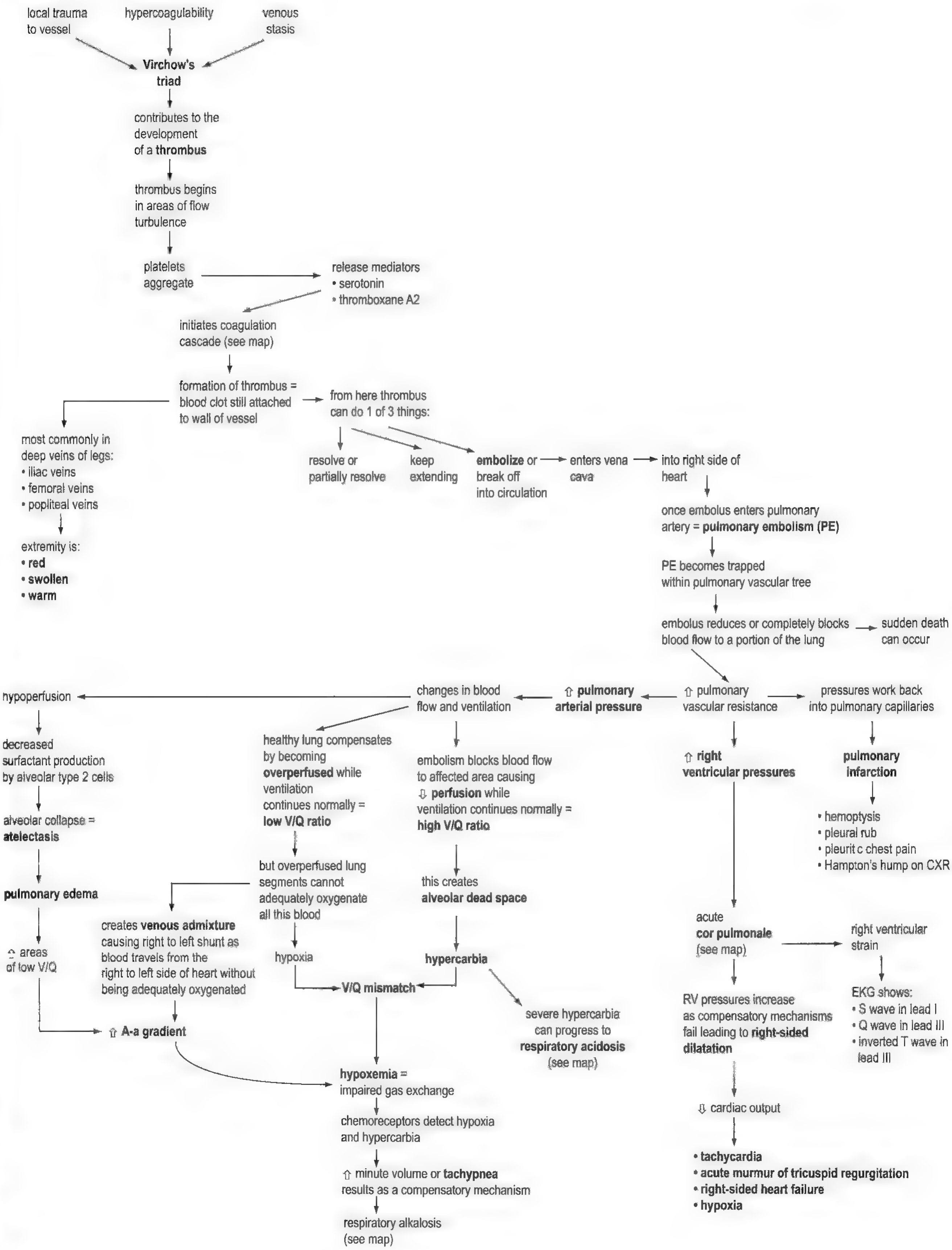
aka status asthmaticus

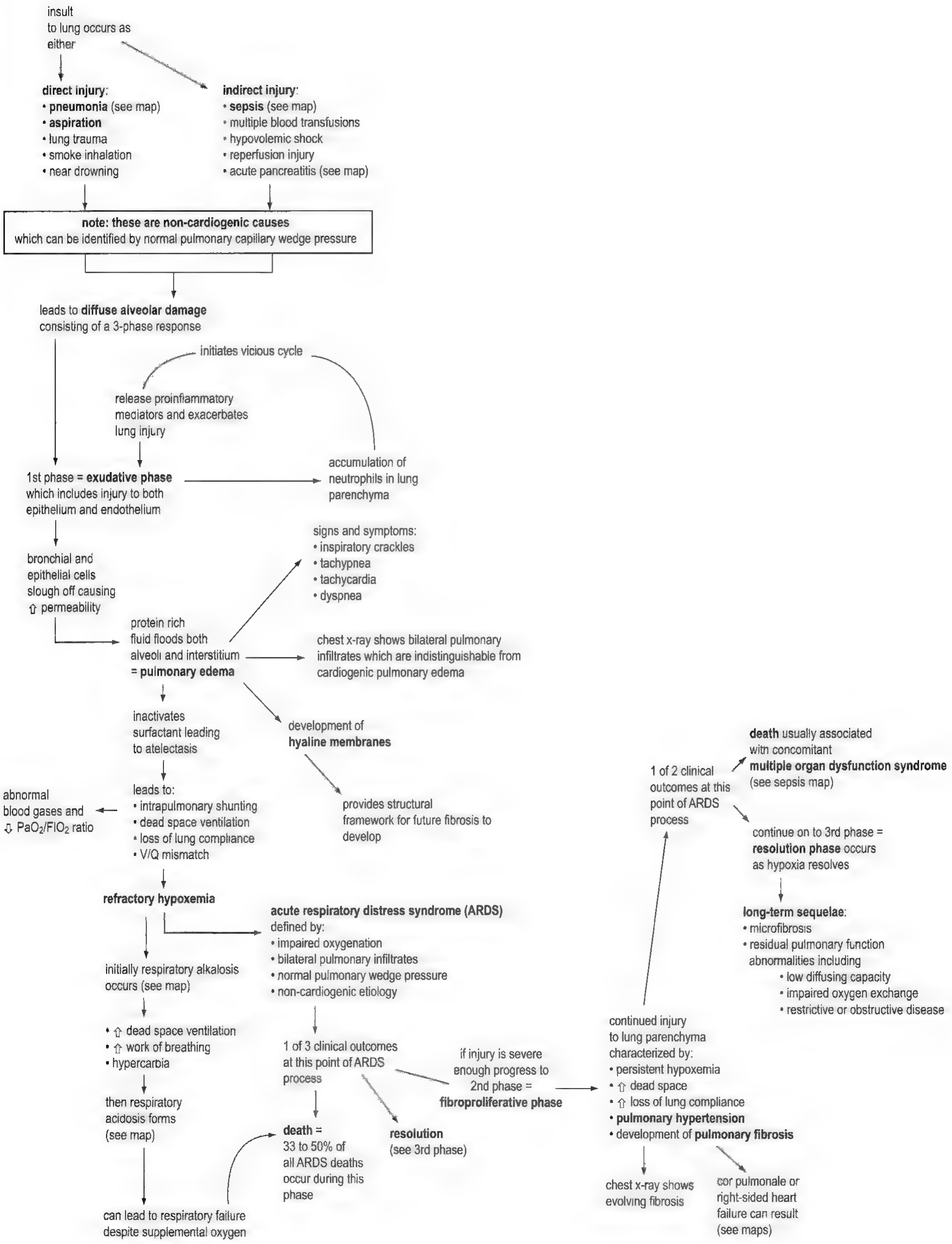
repeated attacks lead to **chronic asthma**

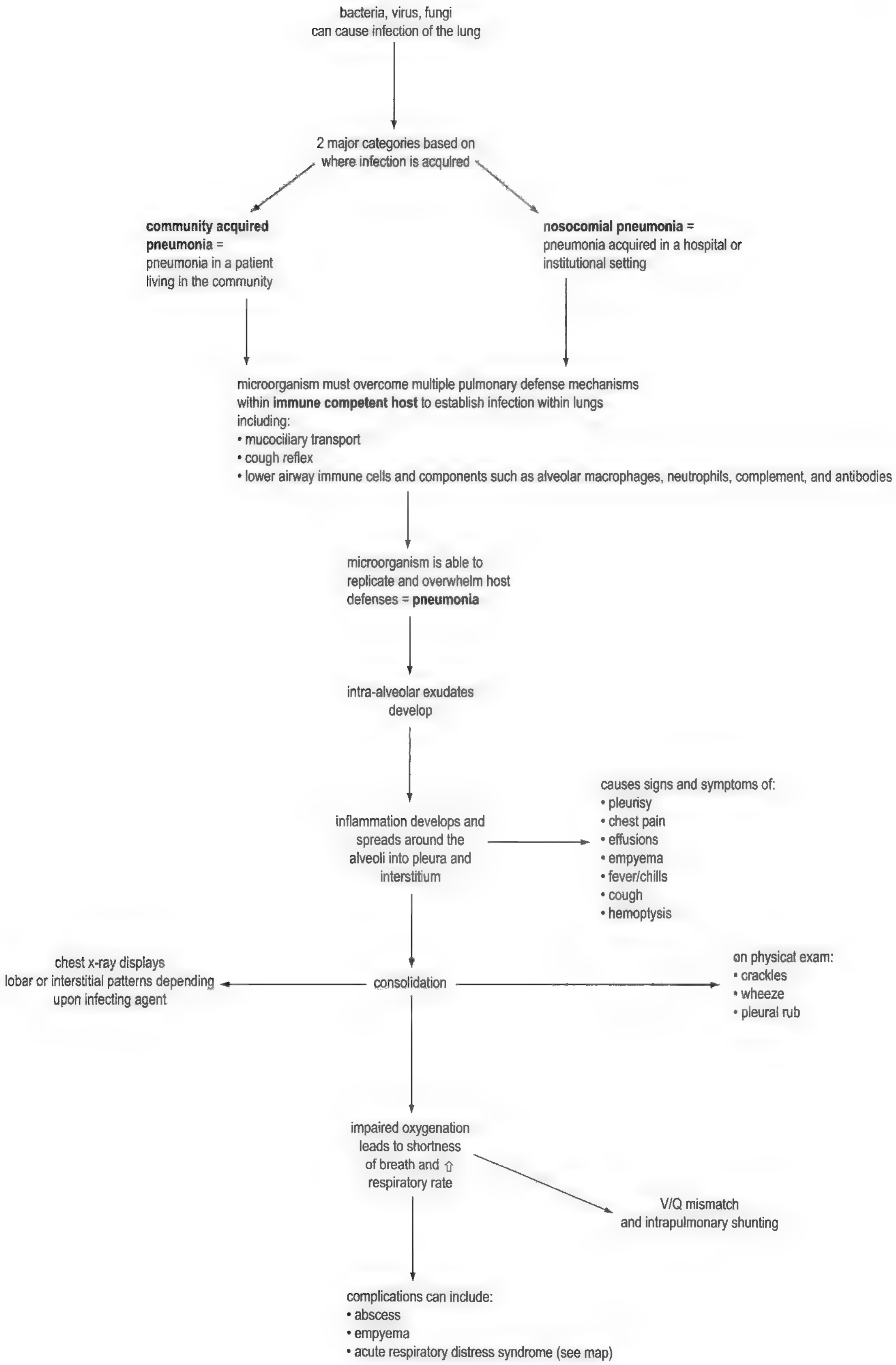
characterized by **airway remodeling =** thickening of small and large airways

due to:
- goblet cell hyperplasia/hypertrophy
- collagen deposition and subepithelial fibrosis
- smooth muscle hyperplasia/hypertrophy
- ⇧ vascularity

causes **nonreversible airway obstruction**


local trauma to vessel
hypercoagulability
venous stasis
Virchow's triad
contributes to the development of a thrombus
thrombus begins in areas of flow turbulence
platelets aggregate
release mediators
• serotonin
• thromboxane A2
initiates coagulation cascade (see map)
formation of thrombus = blood clot still attached to wall of vessel
most commonly in deep veins of legs:
• iliac veins
• femoral veins
• popliteal veins
extremity is:
• red
• swollen
• warm
from here thrombus can do 1 of 3 things:
resolve or partially resolve
keep extending
embolize or break off into circulation
enters vena cava
into right side of heart
once embolus enters pulmonary artery = pulmonary embolism (PE)
PE becomes trapped within pulmonary vascular tree
embolus reduces or completely blocks blood flow to a portion of the lung
sudden death can occur
⇧ pulmonary vascular resistance
pressures work back into pulmonary capillaries
pulmonary infarction
• hemoptysis
• pleural rub
• pleuritic chest pain
• Hampton's hump on CXR
⇧ right ventricular pressures
acute cor pulmonale (see map)
right ventricular strain
EKG shows:
• S wave in lead I
• Q wave in lead III
• inverted T wave in lead III
RV pressures increase as compensatory mechanisms fail leading to right-sided dilatation
⇩ cardiac output
• tachycardia
• acute murmur of tricuspid regurgitation
• right-sided heart failure
• hypoxia
⇧ pulmonary arterial pressure
changes in blood flow and ventilation
hypoperfusion
decreased surfactant production by alveolar type 2 cells
alveolar collapse = atelectasis
pulmonary edema
⇧ areas of low V/Q
healthy lung compensates by becoming overperfused while ventilation continues normally = low V/Q ratio
but overperfused lung segments cannot adequately oxygenate all this blood
creates venous admixture causing right to left shunt as blood travels from the right to left side of heart without being adequately oxygenated
⇧ A-a gradient
hypoxia
embolism blocks blood flow to affected area causing ⇩ perfusion while ventilation continues normally = high V/Q ratio
this creates alveolar dead space
hypercarbia
severe hypercarbia can progress to respiratory acidosis (see map)
V/Q mismatch
hypoxemia = impaired gas exchange
chemoreceptors detect hypoxia and hypercarbia
⇧ minute volume or tachypnea results as a compensatory mechanism
respiratory alkalosis (see map)


insult to lung occurs as either
direct injury:
• pneumonia (see map)
• aspiration
• lung trauma
• smoke inhalation
• near drowning
indirect injury:
• sepsis (see map)
• multiple blood transfusions
• hypovolemic shock
• reperfusion injury
• acute pancreatitis (see map)
note: these are non-cardiogenic causes which can be identified by normal pulmonary capillary wedge pressure
leads to diffuse alveolar damage consisting of a 3-phase response
initiates vicious cycle
release proinflammatory mediators and exacerbates lung injury
1st phase = exudative phase which includes injury to both epithelium and endothelium
accumulation of neutrophils in lung parenchyma
bronchial and epithelial cells slough off causing ⇧ permeability
signs and symptoms:
• inspiratory crackles
• tachypnea
• tachycardia
• dyspnea
protein rich fluid floods both alveoli and interstitium = pulmonary edema
chest x-ray shows bilateral pulmonary infiltrates which are indistinguishable from cardiogenic pulmonary edema
inactivates surfactant leading to atelectasis
development of hyaline membranes
provides structural framework for future fibrosis to develop
leads to:
• intrapulmonary shunting
• dead space ventilation
• loss of lung compliance
• V/Q mismatch
abnormal blood gases and ⇩ PaO_2/FIO_2 ratio
refractory hypoxemia
acute respiratory distress syndrome (ARDS) defined by:
• impaired oxygenation
• bilateral pulmonary infiltrates
• normal pulmonary wedge pressure
• non-cardiogenic etiology
initially respiratory alkalosis occurs (see map)
• ⇧ dead space ventilation
• ⇧ work of breathing
• hypercarbia
then respiratory acidosis forms (see map)
can lead to respiratory failure despite supplemental oxygen
1 of 3 clinical outcomes at this point of ARDS process
death = 33 to 50% of all ARDS deaths occur during this phase
resolution (see 3rd phase)
if injury is severe enough progress to 2nd phase = fibroproliferative phase
continued injury to lung parenchyma characterized by:
• persistent hypoxemia
• ⇧ dead space
• ⇧ loss of lung compliance
• pulmonary hypertension
• development of pulmonary fibrosis
chest x-ray shows evolving fibrosis
cor pulmonale or right-sided heart failure can result (see maps)
1 of 2 clinical outcomes at this point of ARDS process
death usually associated with concomitant multiple organ dysfunction syndrome (see sepsis map)
continue on to 3rd phase = resolution phase occurs as hypoxia resolves
long-term sequelae:
• microfibrosis
• residual pulmonary function abnormalities including
• low diffusing capacity
• impaired oxygen exchange
• restrictive or obstructive disease



bacteria, virus, fungi
can cause infection of the lung

2 major categories based on
where infection is acquired

community acquired pneumonia =
pneumonia in a patient living in the community

nosocomial pneumonia =
pneumonia acquired in a hospital or institutional setting

microorganism must overcome multiple pulmonary defense mechanisms within **immune competent host** to establish infection within lungs including:
- mucociliary transport
- cough reflex
- lower airway immune cells and components such as alveolar macrophages, neutrophils, complement, and antibodies

microorganism is able to replicate and overwhelm host defenses = **pneumonia**

intra-alveolar exudates develop

inflammation develops and spreads around the alveoli into pleura and interstitium

causes signs and symptoms of:
- pleurisy
- chest pain
- effusions
- empyema
- fever/chills
- cough
- hemoptysis

consolidation

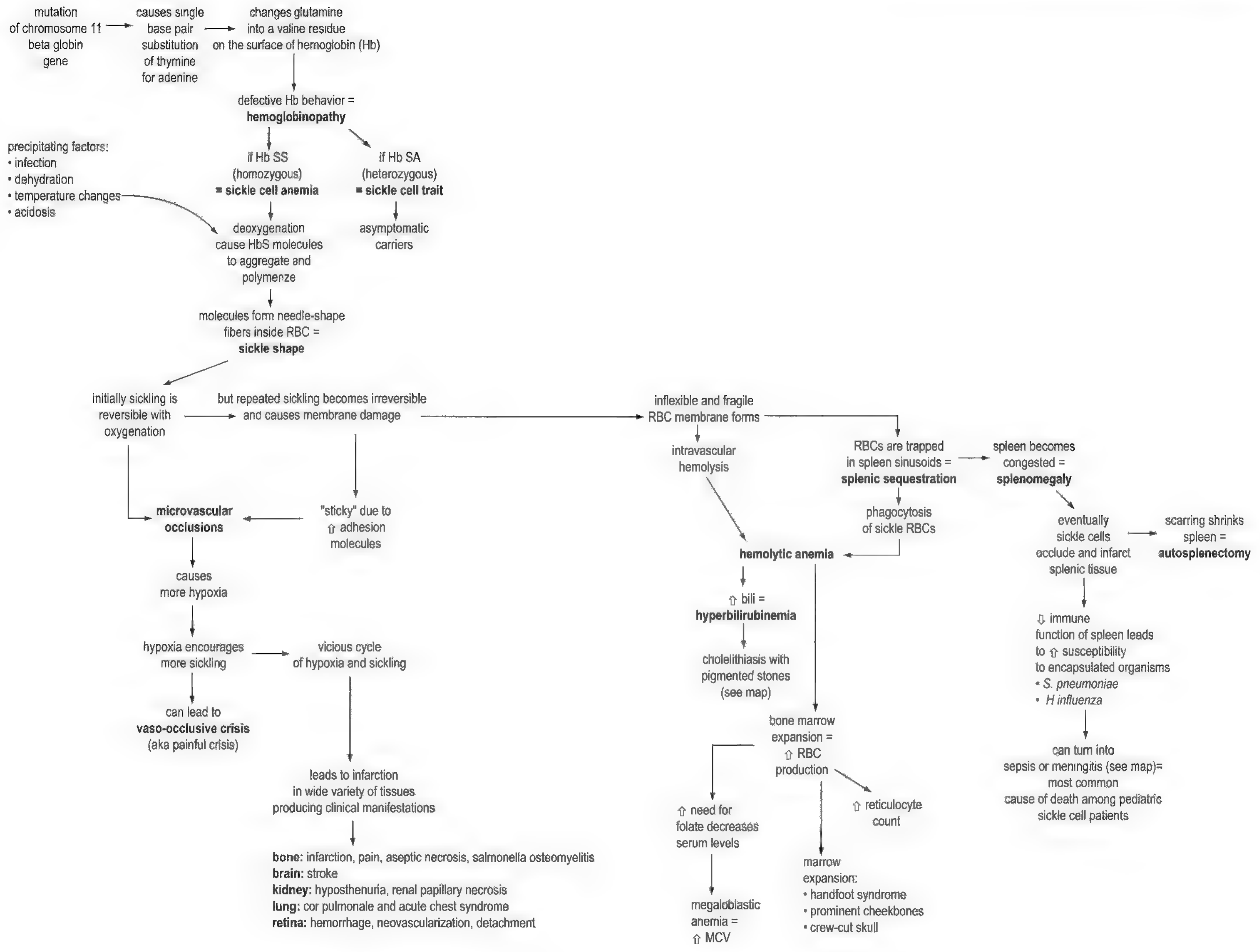
chest x-ray displays
lobar or interstitial patterns depending upon infecting agent

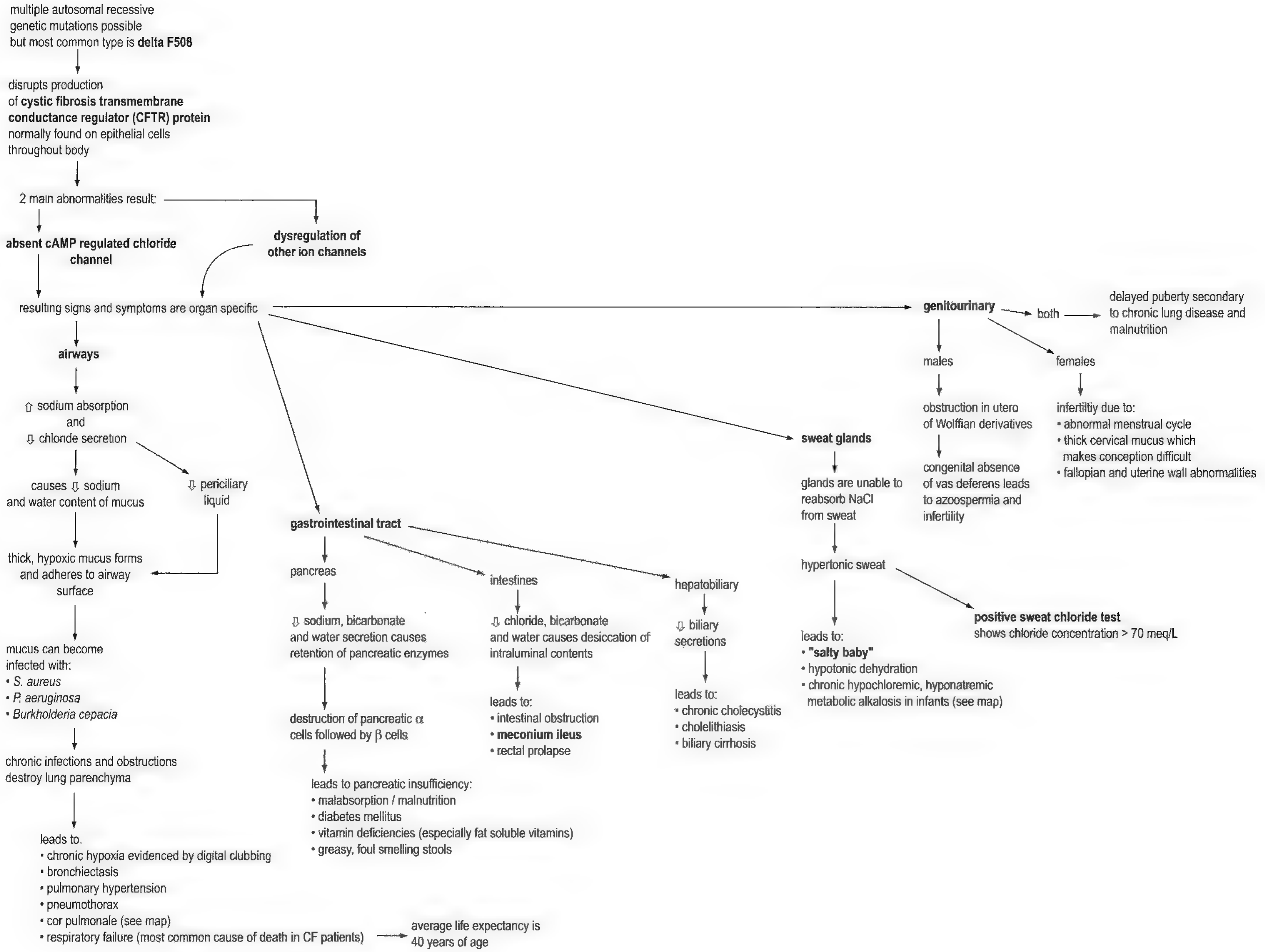
on physical exam:
- crackles
- wheeze
- pleural rub

impaired oxygenation leads to shortness of breath and ⇧ respiratory rate

V/Q mismatch
and intrapulmonary shunting

complications can include:
- abscess
- empyema
- acute respiratory distress syndrome (see map)


mutation of chromosome 11 beta globin gene
causes single base pair substitution of thymine for adenine
changes glutamine into a valine residue on the surface of hemoglobin (Hb)
defective Hb behavior = **hemoglobinopathy**
if Hb SS (homozygous) **= sickle cell anemia**
if Hb SA (heterozygous) **= sickle cell trait**
asymptomatic carriers
precipitating factors:
• infection
• dehydration
• temperature changes
• acidosis
deoxygenation cause HbS molecules to aggregate and polymerize
molecules form needle-shape fibers inside RBC = **sickle shape**
initially sickling is reversible with oxygenation
but repeated sickling becomes irreversible and causes membrane damage
"sticky" due to ⇧ adhesion molecules
microvascular occlusions
causes more hypoxia
hypoxia encourages more sickling
can lead to **vaso-occlusive crisis** (aka painful crisis)
vicious cycle of hypoxia and sickling
leads to infarction in wide variety of tissues producing clinical manifestations
bone: infarction, pain, aseptic necrosis, salmonella osteomyelitis
brain: stroke
kidney: hyposthenuria, renal papillary necrosis
lung: cor pulmonale and acute chest syndrome
retina: hemorrhage, neovascularization, detachment
inflexible and fragile RBC membrane forms
intravascular hemolysis
RBCs are trapped in spleen sinusoids = **splenic sequestration**
spleen becomes congested = **splenomegaly**
phagocytosis of sickle RBCs
hemolytic anemia
⇧ bili = **hyperbilirubinemia**
cholelithiasis with pigmented stones (see map)
bone marrow expansion = ⇧ RBC production
⇧ need for folate decreases serum levels
megaloblastic anemia = ⇧ MCV
⇧ reticulocyte count
marrow expansion:
• handfoot syndrome
• prominent cheekbones
• crew-cut skull
eventually sickle cells occlude and infarct splenic tissue
scarring shrinks spleen = **autosplenectomy**
⇩ immune function of spleen leads to ⇧ susceptibility to encapsulated organisms
• *S. pneumoniae*
• *H influenza*
can turn into sepsis or meningitis (see map)= most common cause of death among pediatric sickle cell patients



multiple autosomal recessive genetic mutations possible but most common type is **delta F508**

disrupts production of **cystic fibrosis transmembrane conductance regulator (CFTR) protein** normally found on epithelial cells throughout body

2 main abnormalities result:

absent cAMP regulated chloride channel

dysregulation of other ion channels

resulting signs and symptoms are organ specific

airways

⇧ sodium absorption and ⇩ chloride secretion

causes ⇩ sodium and water content of mucus

⇩ periciliary liquid

thick, hypoxic mucus forms and adheres to airway surface

mucus can become infected with:
- *S. aureus*
- *P. aeruginosa*
- *Burkholderia cepacia*

chronic infections and obstructions destroy lung parenchyma

leads to:
- chronic hypoxia evidenced by digital clubbing
- bronchiectasis
- pulmonary hypertension
- pneumothorax
- cor pulmonale (see map)
- respiratory failure (most common cause of death in CF patients)

average life expectancy is 40 years of age

gastrointestinal tract

pancreas

⇩ sodium, bicarbonate and water secretion causes retention of pancreatic enzymes

destruction of pancreatic α cells followed by β cells

leads to pancreatic insufficiency:
- malabsorption / malnutrition
- diabetes mellitus
- vitamin deficiencies (especially fat soluble vitamins)
- greasy, foul smelling stools

intestines

⇩ chloride, bicarbonate and water causes desiccation of intraluminal contents

leads to:
- intestinal obstruction
- **meconium ileus**
- rectal prolapse

hepatobiliary

⇩ biliary secretions

leads to:
- chronic cholecystitis
- cholelithiasis
- biliary cirrhosis

sweat glands

glands are unable to reabsorb NaCl from sweat

hypertonic sweat

leads to:
- **"salty baby"**
- hypotonic dehydration
- chronic hypochloremic, hyponatremic metabolic alkalosis in infants (see map)

positive sweat chloride test
shows chloride concentration > 70 meq/L

genitourinary

both

delayed puberty secondary to chronic lung disease and malnutrition

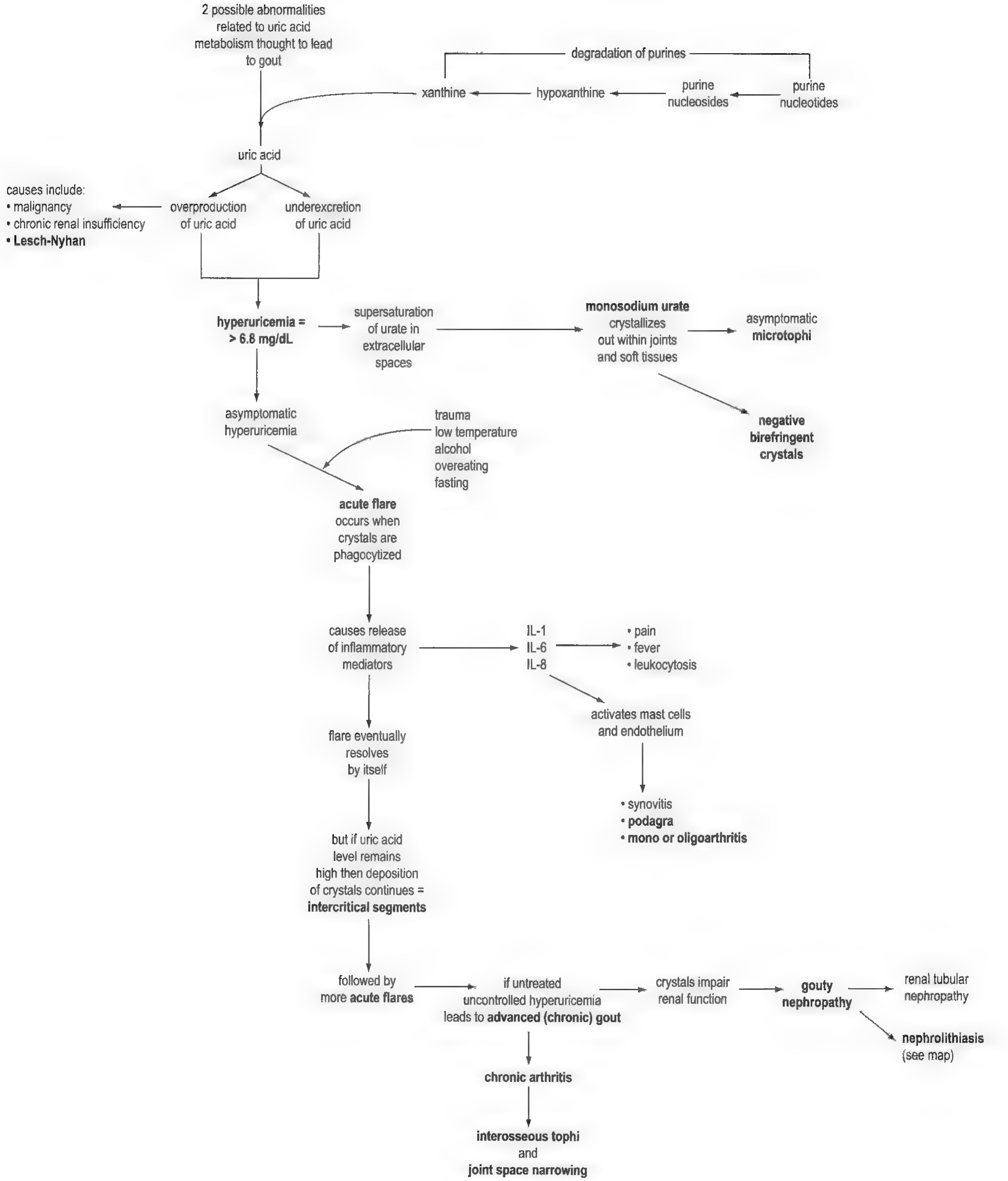
males

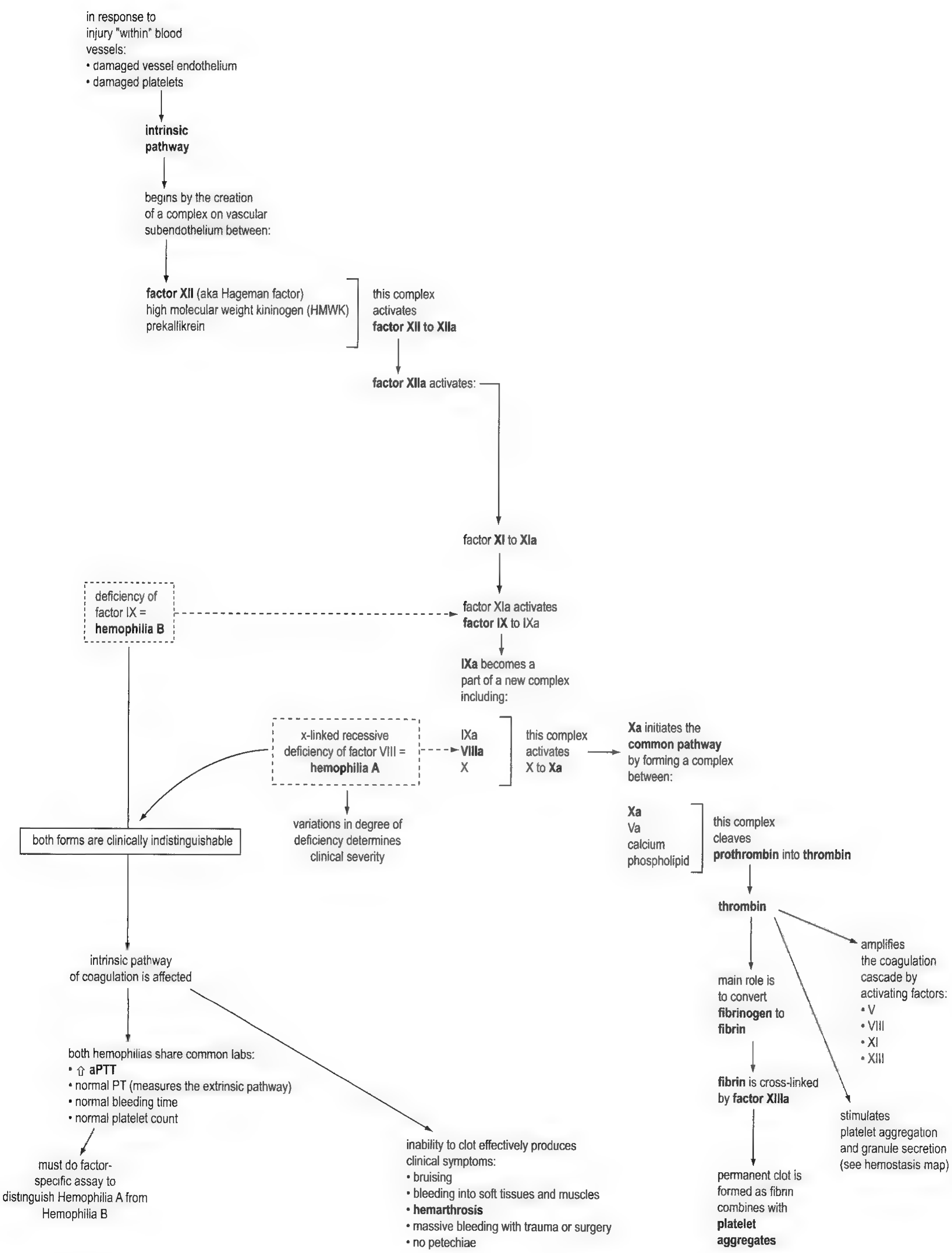
obstruction in utero of Wolffian derivatives

congenital absence of vas deferens leads to azoospermia and infertility

females

infertiltiy due to:
- abnormal menstrual cycle
- thick cervical mucus which makes conception difficult
- fallopian and uterine wall abnormalities


2 possible abnormalities related to uric acid metabolism thought to lead to gout
degradation of purines
xanthine
hypoxanthine
purine nucleosides
purine nucleotides
uric acid
causes include:
• malignancy
• chronic renal insufficiency
• **Lesch-Nyhan**
overproduction of uric acid
underexcretion of uric acid
hyperuricemia = > 6.8 mg/dL
supersaturation of urate in extracellular spaces
monosodium urate crystallizes out within joints and soft tissues
asymptomatic **microtophi**
negative birefringent crystals
asymptomatic hyperuricemia
trauma
low temperature
alcohol
overeating
fasting
acute flare occurs when crystals are phagocytized
causes release of inflammatory mediators
IL-1
IL-6
IL-8
• pain
• fever
• leukocytosis
activates mast cells and endothelium
• synovitis
• **podagra**
• **mono or oligoarthritis**
flare eventually resolves by itself
but if uric acid level remains high then deposition of crystals continues = **intercritical segments**
followed by more **acute flares**
if untreated uncontrolled hyperuricemia leads to **advanced (chronic) gout**
crystals impair renal function
gouty nephropathy
renal tubular nephropathy
nephrolithiasis (see map)
chronic arthritis
interosseous tophi and **joint space narrowing**



in response to injury "within" blood vessels:
- damaged vessel endothelium
- damaged platelets

intrinsic pathway

begins by the creation of a complex on vascular subendothelium between:

factor XII (aka Hageman factor)
high molecular weight kininogen (HMWK)
prekallikrein

this complex activates **factor XII to XIIa**

factor XIIa activates:

factor **XI** to **XIa**

factor XIa activates **factor IX** to IXa

deficiency of factor IX = **hemophilia B**

IXa becomes a part of a new complex including:

IXa
VIIIa
X

this complex activates X to **Xa**

x-linked recessive deficiency of factor VIII = **hemophilia A**

variations in degree of deficiency determines clinical severity

both forms are clinically indistinguishable

Xa initiates the **common pathway** by forming a complex between:

Xa
Va
calcium
phospholipid

this complex cleaves **prothrombin** into **thrombin**

thrombin

main role is to convert **fibrinogen** to **fibrin**

fibrin is cross-linked by **factor XIIIa**

permanent clot is formed as fibrin combines with **platelet aggregates**

amplifies the coagulation cascade by activating factors:
- V
- VIII
- XI
- XIII

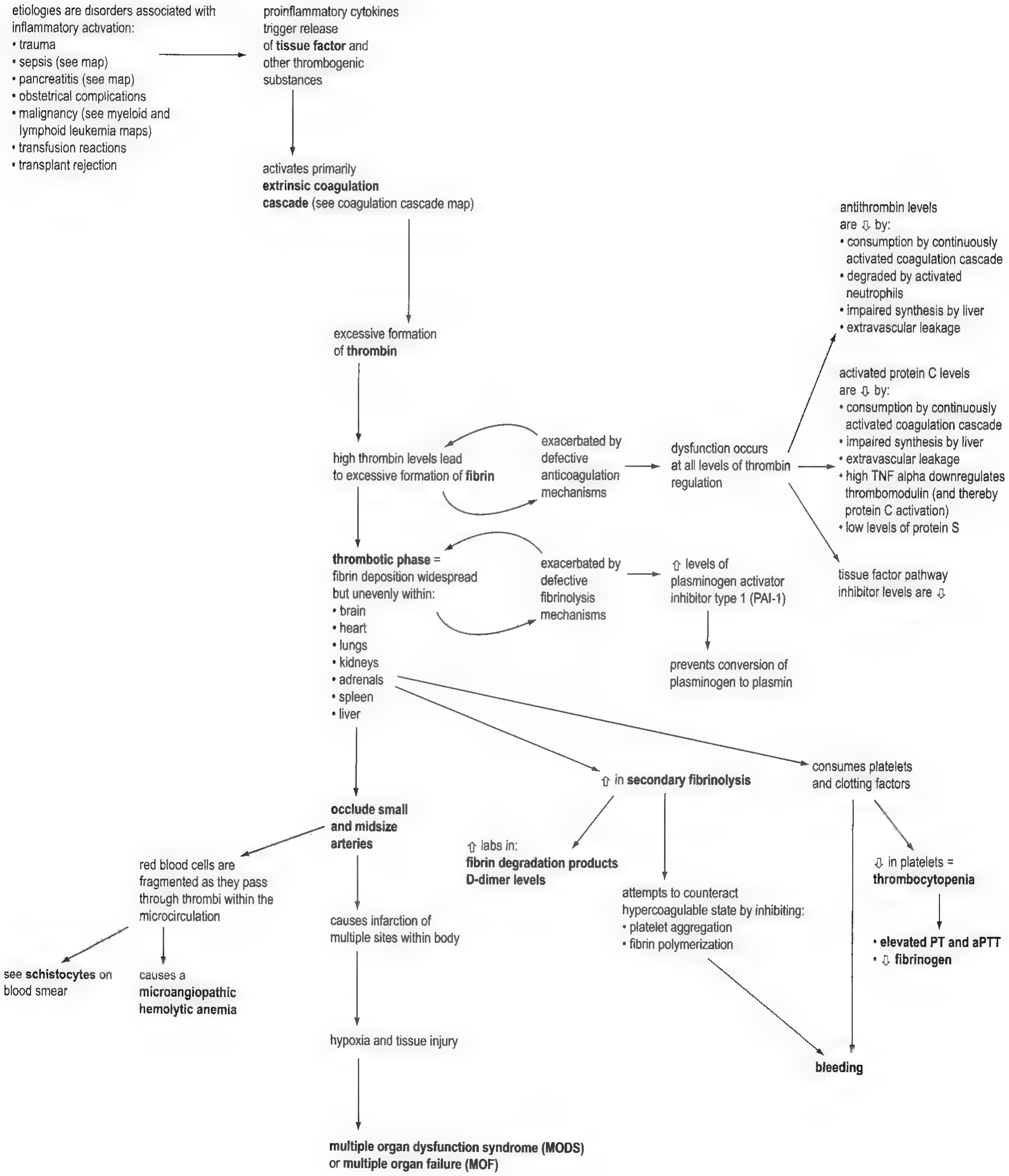
stimulates platelet aggregation and granule secretion (see hemostasis map)

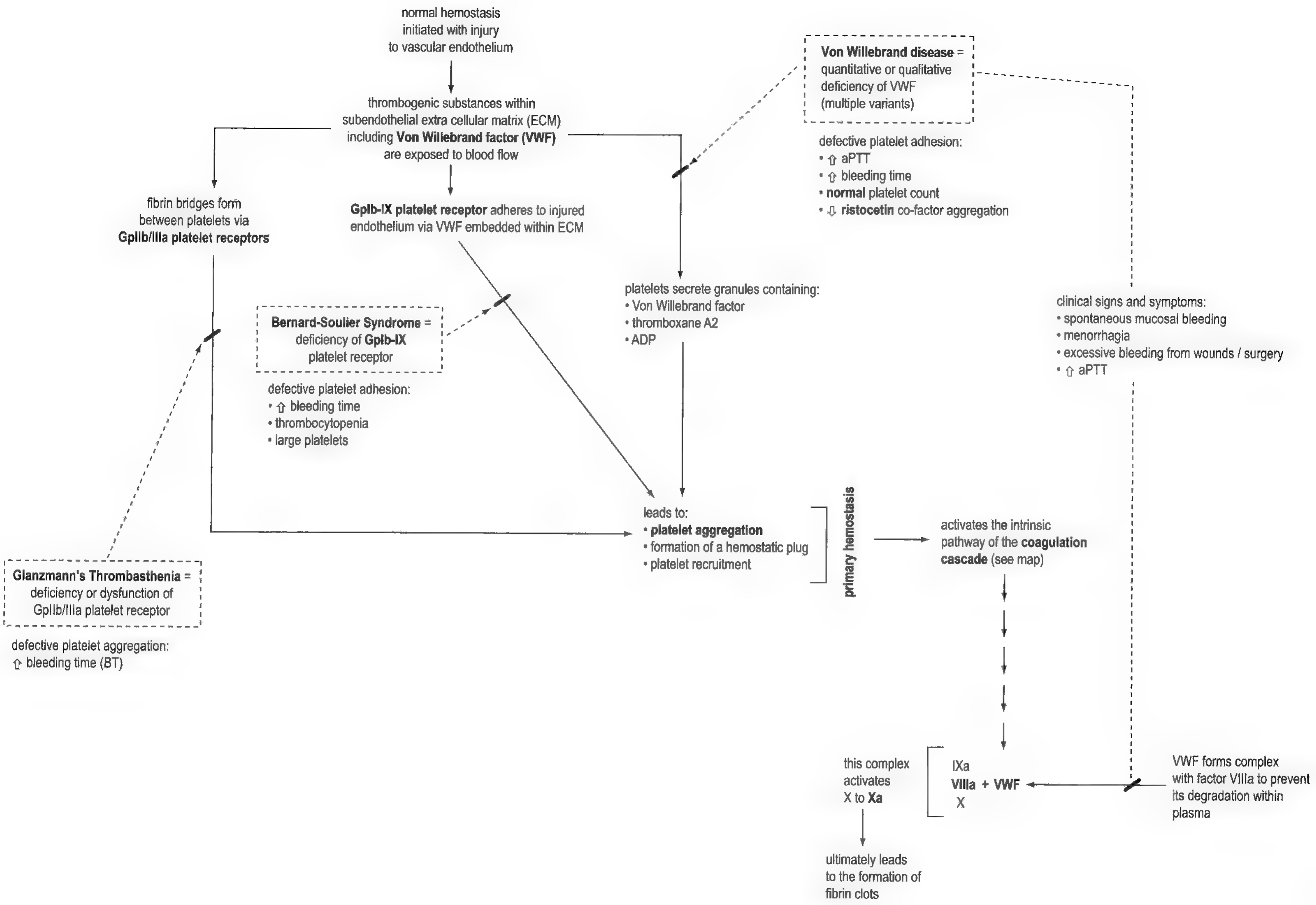
intrinsic pathway of coagulation is affected

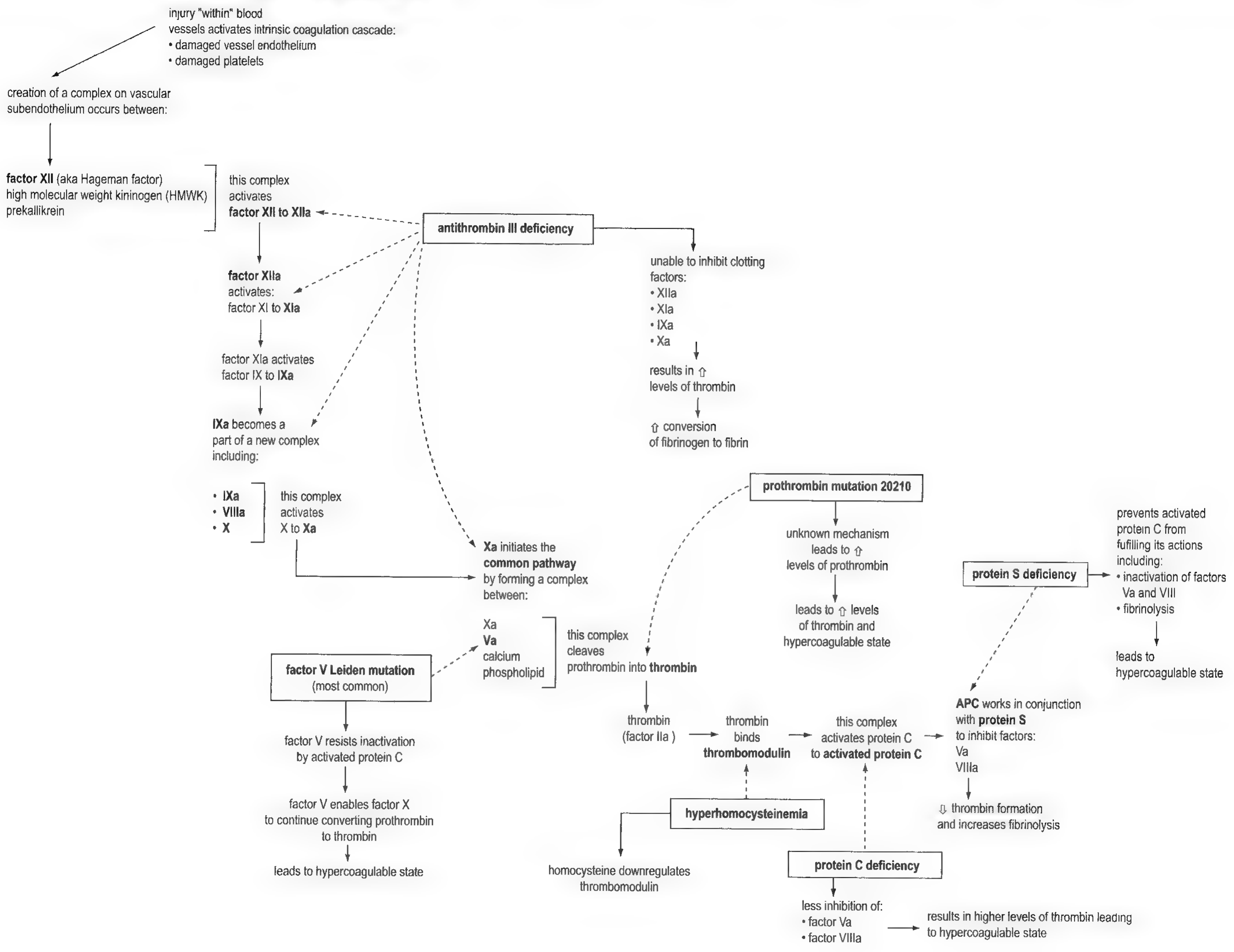
both hemophilias share common labs:
- ⇧ **aPTT**
- normal PT (measures the extrinsic pathway)
- normal bleeding time
- normal platelet count

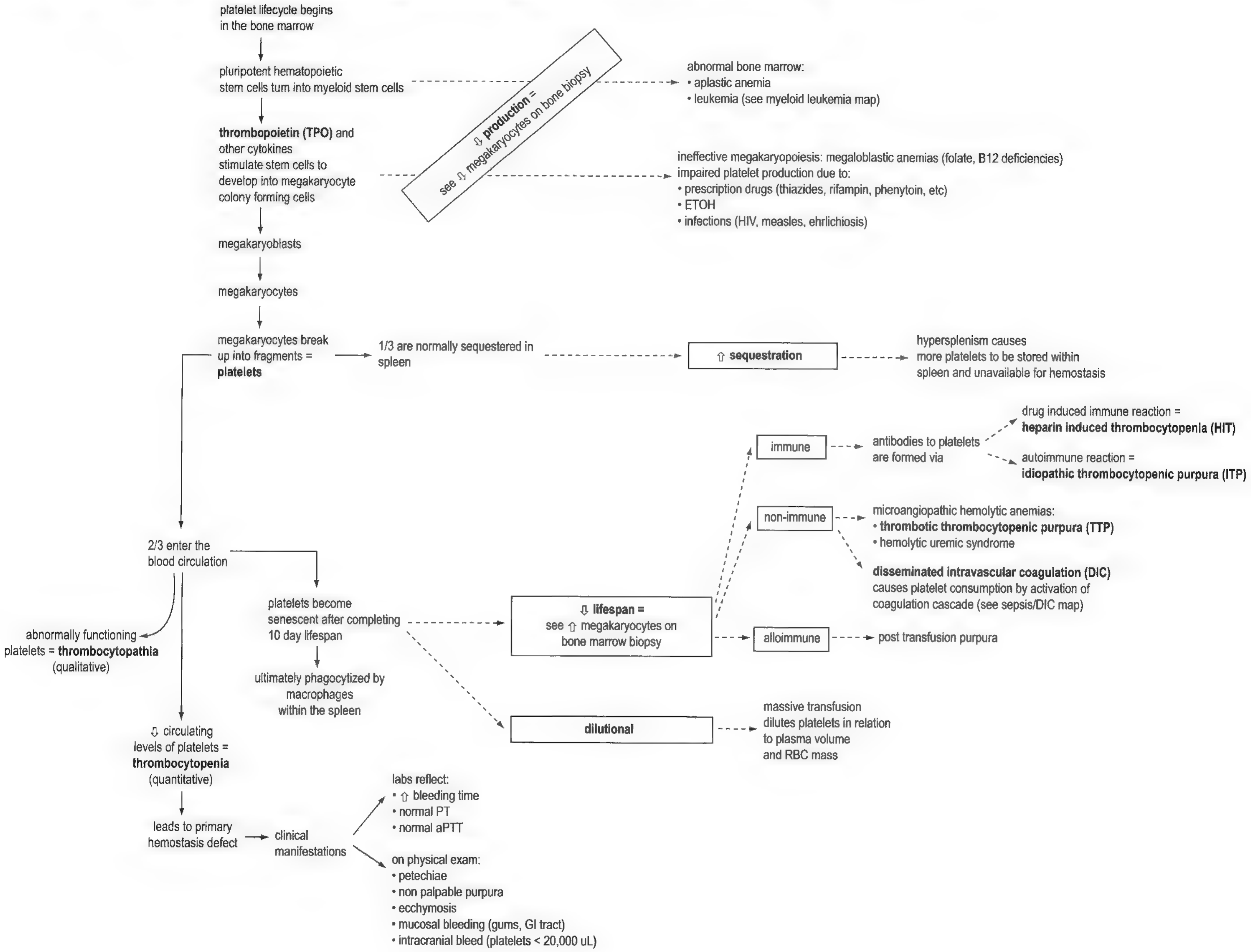
must do factor-specific assay to distinguish Hemophilia A from Hemophilia B

inability to clot effectively produces clinical symptoms:
- bruising
- bleeding into soft tissues and muscles
- **hemarthrosis**
- massive bleeding with trauma or surgery
- no petechiae


etiologies are disorders associated with inflammatory activation: • trauma • sepsis (see map) • pancreatitis (see map) • obstetrical complications • malignancy (see myeloid and lymphoid leukemia maps) • transfusion reactions • transplant rejection
proinflammatory cytokines trigger release of **tissue factor** and other thrombogenic substances
activates primarily **extrinsic coagulation cascade** (see coagulation cascade map)
excessive formation of **thrombin**
high thrombin levels lead to excessive formation of **fibrin**
exacerbated by defective anticoagulation mechanisms
dysfunction occurs at all levels of thrombin regulation
antithrombin levels are ⇩ by: • consumption by continuously activated coagulation cascade • degraded by activated neutrophils • impaired synthesis by liver • extravascular leakage
activated protein C levels are ⇩ by: • consumption by continuously activated coagulation cascade • impaired synthesis by liver • extravascular leakage • high TNF alpha downregulates thrombomodulin (and thereby protein C activation) • low levels of protein S
tissue factor pathway inhibitor levels are ⇩
thrombotic phase = fibrin deposition widespread but unevenly within: • brain • heart • lungs • kidneys • adrenals • spleen • liver
exacerbated by defective fibrinolysis mechanisms
⇧ levels of plasminogen activator inhibitor type 1 (PAI-1)
prevents conversion of plasminogen to plasmin
⇧ in **secondary fibrinolysis**
consumes platelets and clotting factors
occlude small and midsize arteries
red blood cells are fragmented as they pass through thrombi within the microcirculation
see **schistocytes** on blood smear
causes a **microangiopathic hemolytic anemia**
⇧ labs in: **fibrin degradation products D-dimer levels**
attempts to counteract hypercoagulable state by inhibiting: • platelet aggregation • fibrin polymerization
⇩ in platelets = **thrombocytopenia**
• **elevated PT and aPTT** • ⇩ **fibrinogen**
causes infarction of multiple sites within body
hypoxia and tissue injury
bleeding
multiple organ dysfunction syndrome (MODS) or **multiple organ failure (MOF)**


normal hemostasis initiated with injury to vascular endothelium
thrombogenic substances within subendothelial extra cellular matrix (ECM) including **Von Willebrand factor (VWF)** are exposed to blood flow
fibrin bridges form between platelets via **GpIIb/IIIa platelet receptors**
GpIb-IX platelet receptor adheres to injured endothelium via VWF embedded within ECM
Von Willebrand disease = quantitative or qualitative deficiency of VWF (multiple variants)
defective platelet adhesion:
• ⇧ aPTT
• ⇧ bleeding time
• **normal** platelet count
• ⇩ **ristocetin** co-factor aggregation
platelets secrete granules containing:
• Von Willebrand factor
• thromboxane A2
• ADP
Bernard-Soulier Syndrome = deficiency of **GpIb-IX** platelet receptor
defective platelet adhesion:
• ⇧ bleeding time
• thrombocytopenia
• large platelets
clinical signs and symptoms:
• spontaneous mucosal bleeding
• menorrhagia
• excessive bleeding from wounds / surgery
• ⇧ aPTT
leads to:
• **platelet aggregation**
• formation of a hemostatic plug
• platelet recruitment
primary hemostasis
activates the intrinsic pathway of the **coagulation cascade** (see map)
Glanzmann's Thrombasthenia = deficiency or dysfunction of GpIIb/IIIa platelet receptor
defective platelet aggregation:
⇧ bleeding time (BT)
this complex activates X to **Xa**
IXa
VIIIa + **VWF**
X
VWF forms complex with factor VIIIa to prevent its degradation within plasma
ultimately leads to the formation of fibrin clots


injury "within" blood vessels activates intrinsic coagulation cascade:
• damaged vessel endothelium
• damaged platelets
creation of a complex on vascular subendothelium occurs between:
factor XII (aka Hageman factor)
high molecular weight kininogen (HMWK)
prekallikrein
this complex activates factor XII to XIIa
factor XIIa activates: factor XI to XIa
factor XIa activates factor IX to IXa
IXa becomes a part of a new complex including:
• IXa
• VIIIa
• X
this complex activates X to Xa
Xa initiates the common pathway by forming a complex between:
Xa
Va
calcium
phospholipid
this complex cleaves prothrombin into thrombin
thrombin (factor IIa)
thrombin binds thrombomodulin
this complex activates protein C to activated protein C
APC works in conjunction with protein S to inhibit factors:
Va
VIIIa
⇩ thrombin formation and increases fibrinolysis
antithrombin III deficiency
unable to inhibit clotting factors:
• XIIa
• XIa
• IXa
• Xa
results in ⇧ levels of thrombin
⇧ conversion of fibrinogen to fibrin
factor V Leiden mutation (most common)
factor V resists inactivation by activated protein C
factor V enables factor X to continue converting prothrombin to thrombin
leads to hypercoagulable state
prothrombin mutation 20210
unknown mechanism leads to ⇧ levels of prothrombin
leads to ⇧ levels of thrombin and hypercoagulable state
hyperhomocysteinemia
homocysteine downregulates thrombomodulin
protein C deficiency
less inhibition of:
• factor Va
• factor VIIIa
results in higher levels of thrombin leading to hypercoagulable state
protein S deficiency
prevents activated protein C from fufilling its actions including:
• inactivation of factors Va and VIII
• fibrinolysis
leads to hypercoagulable state


platelet lifecycle begins in the bone marrow
pluripotent hematopoietic stem cells turn into myeloid stem cells
thrombopoietin (TPO) and other cytokines stimulate stem cells to develop into megakaryocyte colony forming cells
megakaryoblasts
megakaryocytes
megakaryocytes break up into fragments = platelets
⇩ production = see ⇩ megakaryocytes on bone biopsy
abnormal bone marrow:
• aplastic anemia
• leukemia (see myeloid leukemia map)
ineffective megakaryopoiesis: megaloblastic anemias (folate, B12 deficiencies)
impaired platelet production due to:
• prescription drugs (thiazides, rifampin, phenytoin, etc)
• ETOH
• infections (HIV, measles, ehrlichiosis)
1/3 are normally sequestered in spleen
⇧ sequestration
hypersplenism causes more platelets to be stored within spleen and unavailable for hemostasis
2/3 enter the blood circulation
abnormally functioning platelets = thrombocytopathia (qualitative)
platelets become senescent after completing 10 day lifespan
ultimately phagocytized by macrophages within the spleen
⇩ lifespan = see ⇧ megakaryocytes on bone marrow biopsy
immune
antibodies to platelets are formed via
drug induced immune reaction = heparin induced thrombocytopenia (HIT)
autoimmune reaction = idiopathic thrombocytopenic purpura (ITP)
non-immune
microangiopathic hemolytic anemias:
• thrombotic thrombocytopenic purpura (TTP)
• hemolytic uremic syndrome
disseminated intravascular coagulation (DIC) causes platelet consumption by activation of coagulation cascade (see sepsis/DIC map)
alloimmune
post transfusion purpura
dilutional
massive transfusion dilutes platelets in relation to plasma volume and RBC mass
⇩ circulating levels of platelets = thrombocytopenia (quantitative)
leads to primary hemostasis defect
clinical manifestations
labs reflect:
• ⇧ bleeding time
• normal PT
• normal aPTT
on physical exam:
• petechiae
• non palpable purpura
• ecchymosis
• mucosal bleeding (gums, GI tract)
• intracranial bleed (platelets < 20,000 uL)

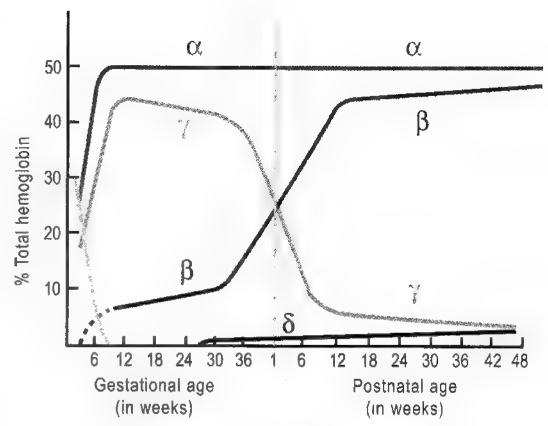
Hemoglobin A (adult hemoglobin) is composed of:
- **2 α chains**
- 2 β chains

α **globin chains** are produced under the direction of 4 α globin genes

genetic mutations result in abnormal α globin chain synthesis

defective hemoglobin synthesis causing a hypochromic anemia = **alpha thalassemia**

mutations can affect between 1 to all 4 α globin genes



Hemoglobin production timeline

if 1 out of 4 α globin genes is defective or absent

silent carrier (α thalassemia-2 trait)

asymptomatic with normal CBC

if 2 out of 4 α globin genes are defective or absent

α thalassemia minor (aka α thalassemia-1 trait)

mild hypochromic microcytic anemia

anemia can resemble β thalassemia minor (see map)

symptomatic in utero as α chains needed for HbF

if 3 out of 4 α globin genes are defective or absent

hemoglobin H disease

moderate to severe disease

allows unpaired β globin chains to accumulate

β globin chains form a tetramer = **HbH**

HbH precipitates and forms **Heinz bodies**

abnormal red blood cells are sequestered by spleen

splenomegaly

hemolytic anemia

ineffective erythropoiesis

leads to some bone marrow hyperplasia

some variants have bony deformities and extramedullary erythropoiesis

if 4 out of 4 α globin genes are defective or absent

hydrops fetalis (aka **Barts hemoglobin** or α **thalassemia major**)

complete absence of α globin chains allows delta globin chains to accumulate

delta chains form tetramer = **Hb Barts**

Hb Barts has high affinity for oxygen

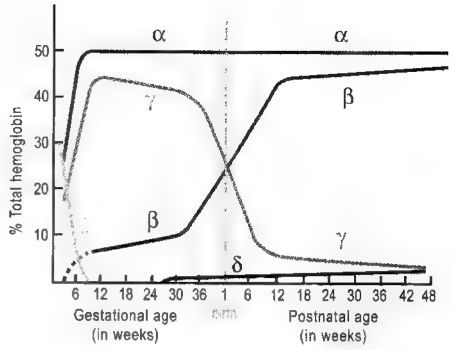
does not release oxygen to fetal tissues

death in utero due to:
- hypoxia
- hydrops fetalis (edema)
- CHF

Hemoglobin A (adult hemoglobin) is composed of:
- 2 α chains
- **2 β chains**

β globin chains are produced under the direction of 2 β globin genes

defective β globin chain production causes a hypochromic anemia = **β thalassemia**



Hemoglobin production timeline

multiple possible genetic mutations results in abnormal β globin chain synthesis

mutations can affect 1 or both β genes

one β globin gene affected

β thalassemia minor (aka **β thalassemia trait**)

single β globin gene produces all β globin chains

but less than normal amount of β globin chains available for hemoglobin synthesis

usually asymptomatic with mild microcytic anemia

both β globin genes affected

β thalassemia intermedia

one of two affected β globin genes is only "mildly" mutated

⇩ but not totally absent β globin chain production

leads to heterogeneous clinical presentation due to wide variety of mutations

inadequate levels of β globin chains for normal hemoglobin synthesis contributes to the α : β globin chain imbalance

β thalassemia major (aka **Cooley's anemia**)

both β globin genes are severely affected by mutation

most severe form of disease requiring lifelong transfusions

while α globin chains production continues normally

excess of normal α globin chains relative to abnormal or absent β chains

both types of mutation and degree of this imbalance determine clinical phenotype

clinical onset begins at 3 to 6 months when **fetal hemoglobin** production stops and no longer masks abnormality

⇩ Hb A production = **moderate to severe anemia**

⇩ oxygen carrying capacity

hypoxia stimulates erythropoiesis in both bone marrow and extramedullary sites such as liver and spleen

bone marrow expansion causes:
- fractures (especially long bones)
- frontal bossing
- maxillary marrow hyperplasia (chipmunk facies)

some α chains cannot find β chains to pair up with

unpaired α chains form intracellular precipitates which accumulate as **inclusion bodies**

inclusion bodies cause oxidative damage to RBC membrane

ineffective erythropoiesis

stimulates ⇧ iron absorption

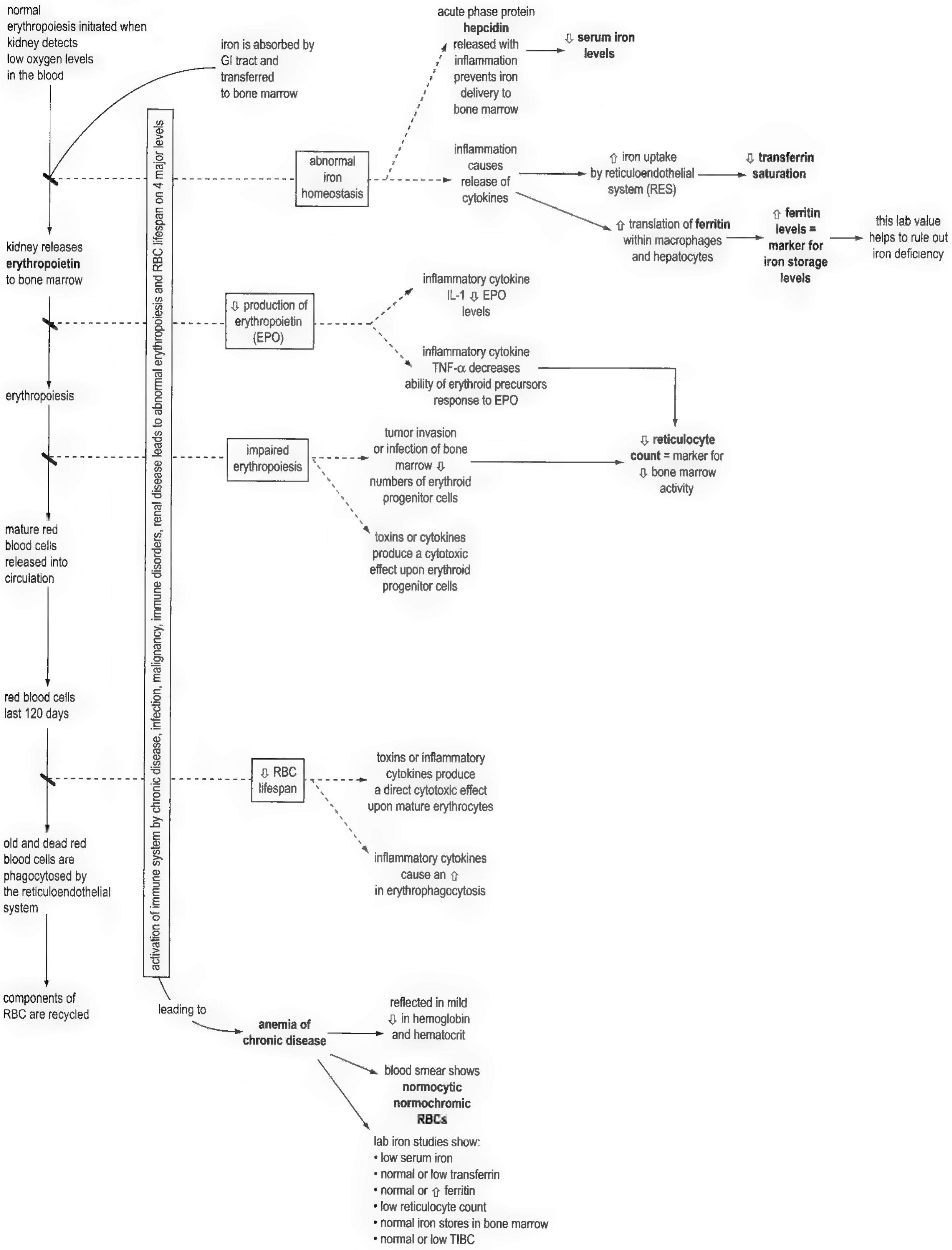
hemochromatosis (see map)

intravascular hemolysis

microcytic hypochromic hemolytic **anemia**

deformed red blood cells are sequestered in spleen = **splenomegaly**

abnormal blood smear shows:
- inclusions bodies
- target cells
- bizarre cells
- anisocytosis



normal erythropoiesis initiated when kidney detects low oxygen levels in the blood

iron is absorbed by GI tract and transferred to bone marrow

kidney releases **erythropoietin** to bone marrow

erythropoiesis

mature red blood cells released into circulation

red blood cells last 120 days

old and dead red blood cells are phagocytosed by the reticuloendothelial system

components of RBC are recycled

activation of immune system by chronic disease, infection, malignancy, immune disorders, renal disease leads to abnormal erythropoiesis and RBC lifespan on 4 major levels

abnormal iron homeostasis

acute phase protein **hepcidin** released with inflammation prevents iron delivery to bone marrow → **⇩ serum iron levels**

inflammation causes release of cytokines → ⇧ iron uptake by reticuloendothelial system (RES) → **⇩ transferrin saturation**

inflammation causes release of cytokines → ⇧ translation of **ferritin** within macrophages and hepatocytes → **⇧ ferritin levels = marker for iron storage levels** → this lab value helps to rule out iron deficiency

⇩ production of erythropoietin (EPO)

inflammatory cytokine IL-1 ⇩ EPO levels

inflammatory cytokine TNF-α decreases ability of erythroid precursors response to EPO → **⇩ reticulocyte count** = marker for ⇩ bone marrow activity

impaired erythropoiesis

tumor invasion or infection of bone marrow ⇩ numbers of erythroid progenitor cells → **⇩ reticulocyte count** = marker for ⇩ bone marrow activity

toxins or cytokines produce a cytotoxic effect upon erythroid progenitor cells

⇩ RBC lifespan

toxins or inflammatory cytokines produce a direct cytotoxic effect upon mature erythrocytes

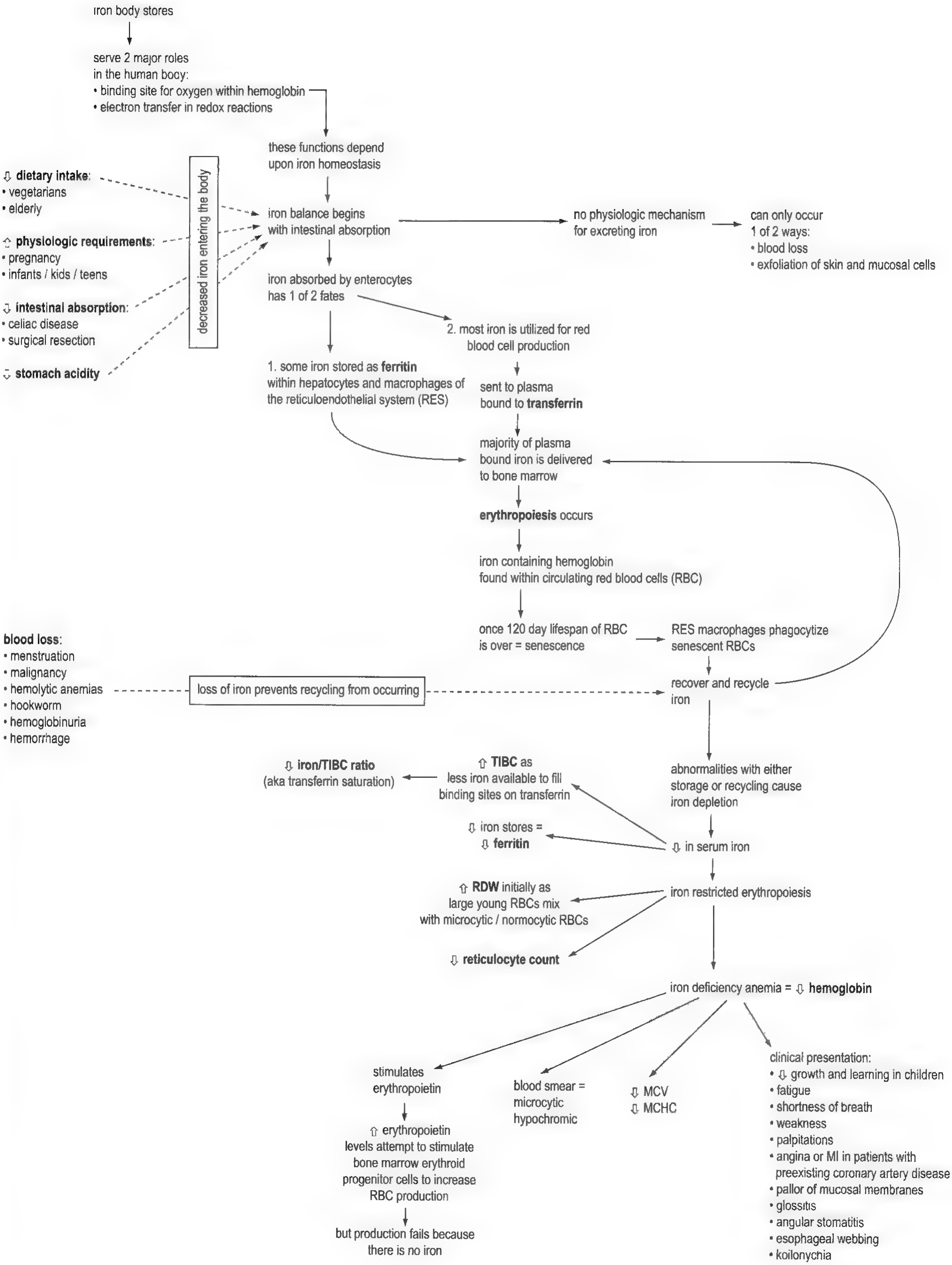
inflammatory cytokines cause an ⇧ in erythrophagocytosis

leading to **anemia of chronic disease**

reflected in mild ⇩ in hemoglobin and hematocrit

blood smear shows **normocytic normochromic RBCs**

lab iron studies show:
- low serum iron
- normal or low transferrin
- normal or ⇧ ferritin
- low reticulocyte count
- normal iron stores in bone marrow
- normal or low TIBC



iron body stores

serve 2 major roles in the human body:
- binding site for oxygen within hemoglobin
- electron transfer in redox reactions

these functions depend upon iron homeostasis

iron balance begins with intestinal absorption

no physiologic mechanism for excreting iron

can only occur 1 of 2 ways:
- blood loss
- exfoliation of skin and mucosal cells

decreased iron entering the body

⇩ **dietary intake**:
- vegetarians
- elderly

⇧ **physiologic requirements**:
- pregnancy
- infants / kids / teens

⇩ **intestinal absorption**:
- celiac disease
- surgical resection

⇩ **stomach acidity**

iron absorbed by enterocytes has 1 of 2 fates

1. some iron stored as **ferritin** within hepatocytes and macrophages of the reticuloendothelial system (RES)

2. most iron is utilized for red blood cell production

sent to plasma bound to **transferrin**

majority of plasma bound iron is delivered to bone marrow

erythropoiesis occurs

iron containing hemoglobin found within circulating red blood cells (RBC)

once 120 day lifespan of RBC is over = senescence

RES macrophages phagocytize senescent RBCs

recover and recycle iron

blood loss:
- menstruation
- malignancy
- hemolytic anemias
- hookworm
- hemoglobinuria
- hemorrhage

loss of iron prevents recycling from occurring

abnormalities with either storage or recycling cause iron depletion

⇩ in serum iron

⇧ **TIBC** as less iron available to fill binding sites on transferrin

⇩ **iron/TIBC ratio** (aka transferrin saturation)

⇩ iron stores = ⇩ **ferritin**

iron restricted erythropoiesis

⇧ **RDW** initially as large young RBCs mix with microcytic / normocytic RBCs

⇩ **reticulocyte count**

iron deficiency anemia = ⇩ **hemoglobin**

stimulates erythropoietin

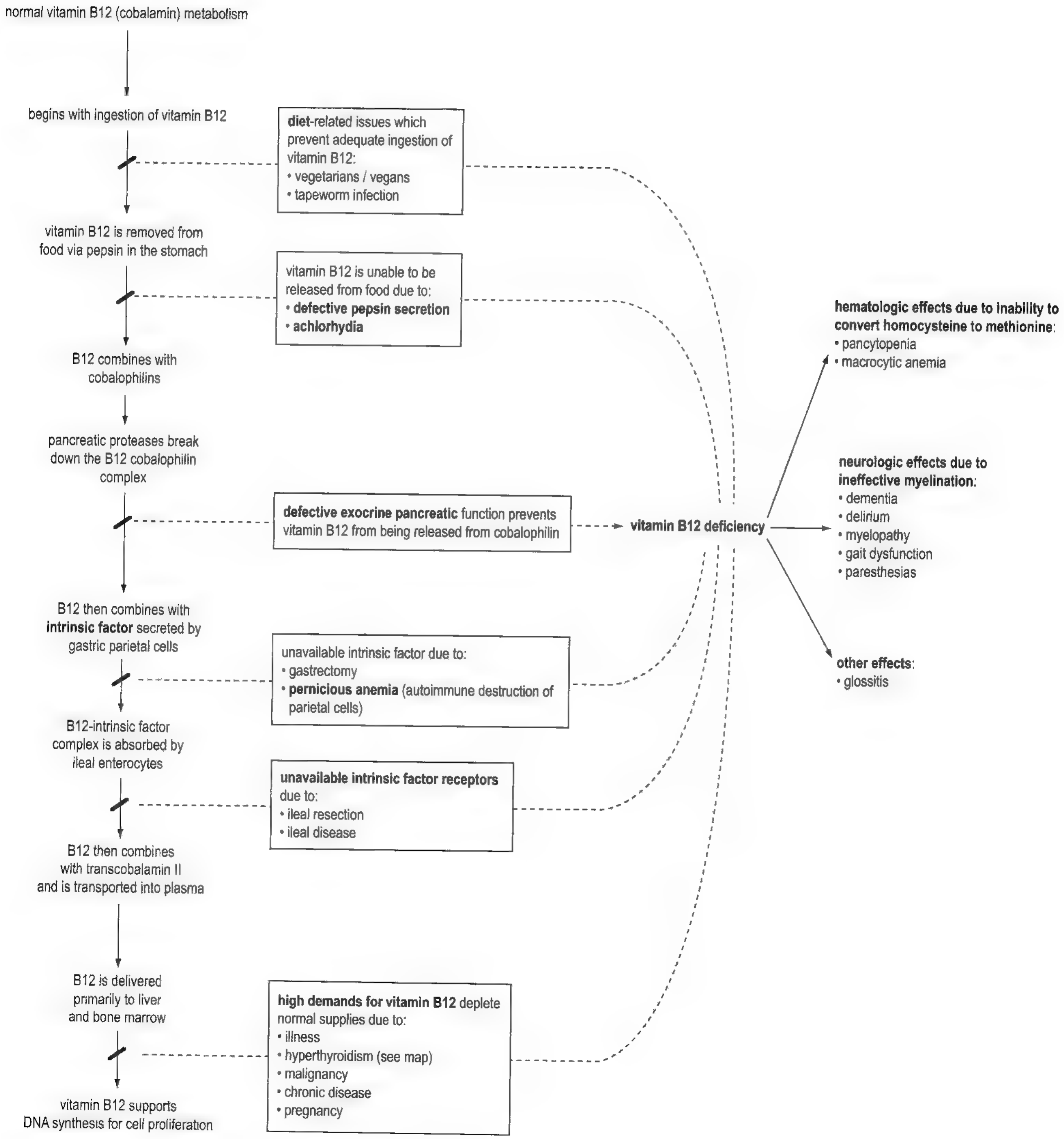
⇧ erythropoietin levels attempt to stimulate bone marrow erythroid progenitor cells to increase RBC production

but production fails because there is no iron

blood smear = microcytic hypochromic

⇩ MCV
⇩ MCHC

clinical presentation:
- ⇩ growth and learning in children
- fatigue
- shortness of breath
- weakness
- palpitations
- angina or MI in patients with preexisting coronary artery disease
- pallor of mucosal membranes
- glossitis
- angular stomatitis
- esophageal webbing
- koilonychia



normal vitamin B12 (cobalamin) metabolism

begins with ingestion of vitamin B12

diet-related issues which prevent adequate ingestion of vitamin B12:
- vegetarians / vegans
- tapeworm infection

vitamin B12 is removed from food via pepsin in the stomach

vitamin B12 is unable to be released from food due to:
- **defective pepsin secretion**
- **achlorhydia**

B12 combines with cobalophilins

pancreatic proteases break down the B12 cobalophilin complex

defective exocrine pancreatic function prevents vitamin B12 from being released from cobalophilin

B12 then combines with **intrinsic factor** secreted by gastric parietal cells

unavailable intrinsic factor due to:
- gastrectomy
- **pernicious anemia** (autoimmune destruction of parietal cells)

B12-intrinsic factor complex is absorbed by ileal enterocytes

unavailable intrinsic factor receptors due to:
- ileal resection
- ileal disease

B12 then combines with transcobalamin II and is transported into plasma

B12 is delivered primarily to liver and bone marrow

high demands for vitamin B12 deplete normal supplies due to:
- illness
- hyperthyroidism (see map)
- malignancy
- chronic disease
- pregnancy

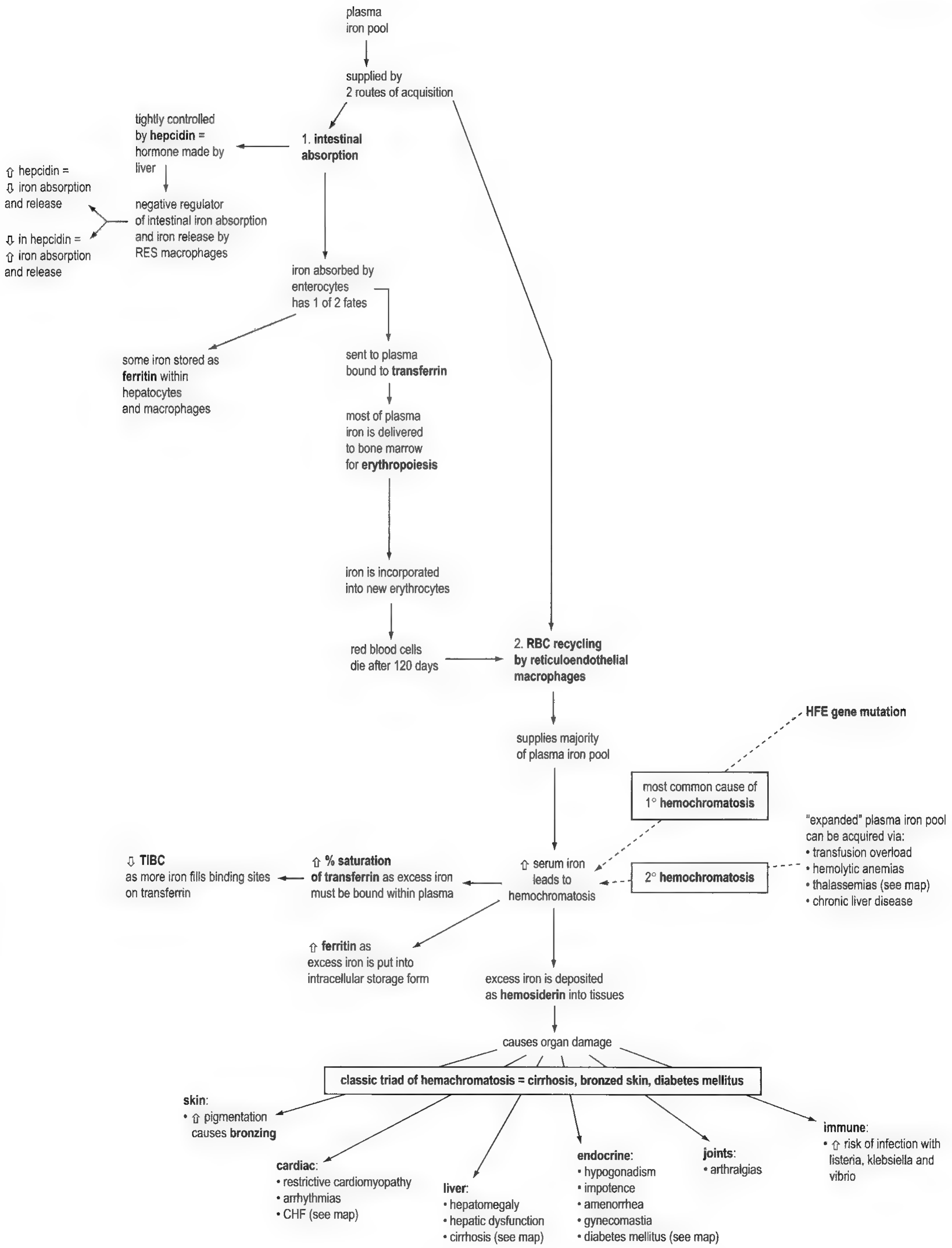
vitamin B12 supports DNA synthesis for cell proliferation

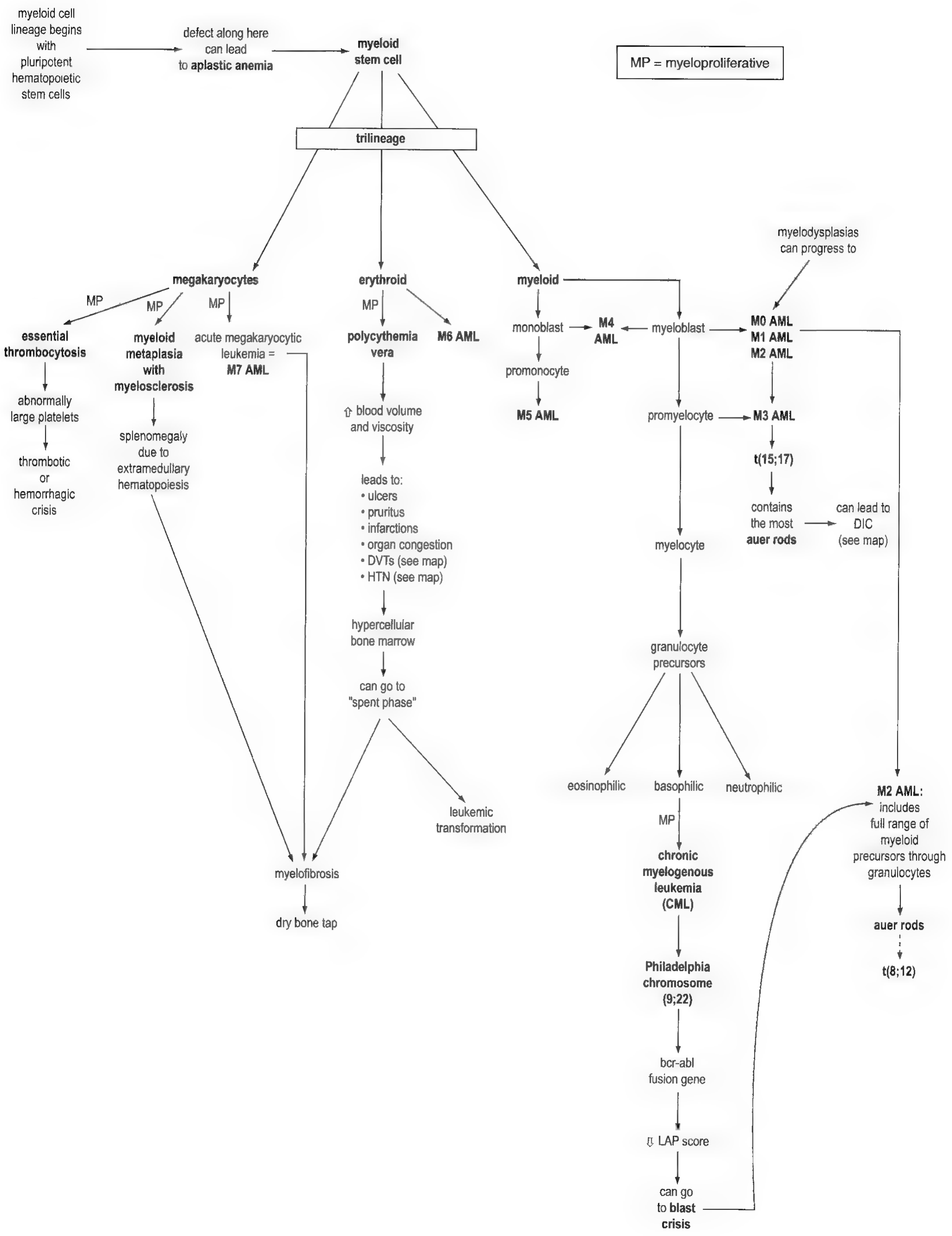
vitamin B12 deficiency

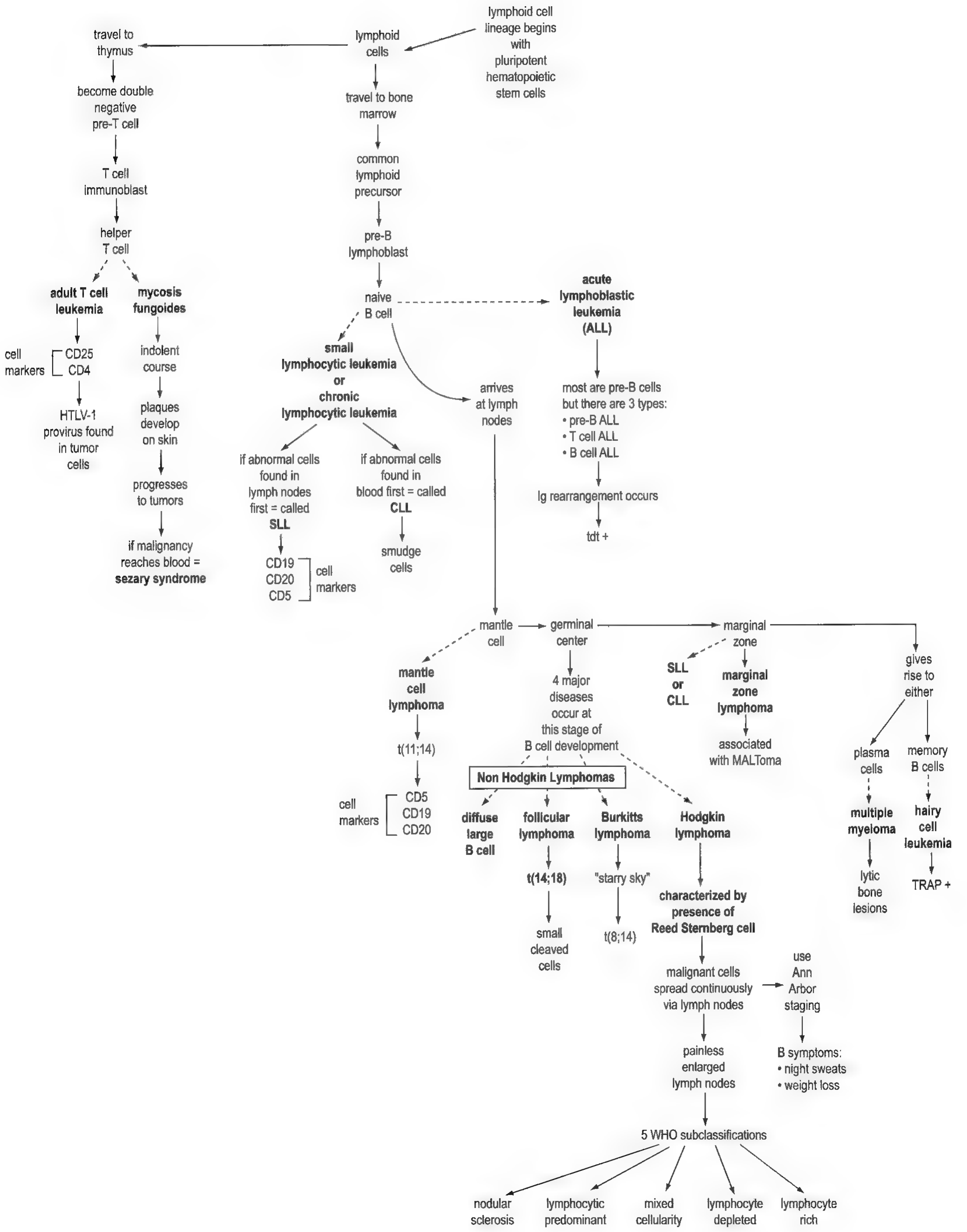
hematologic effects due to inability to convert homocysteine to methionine:
- pancytopenia
- macrocytic anemia

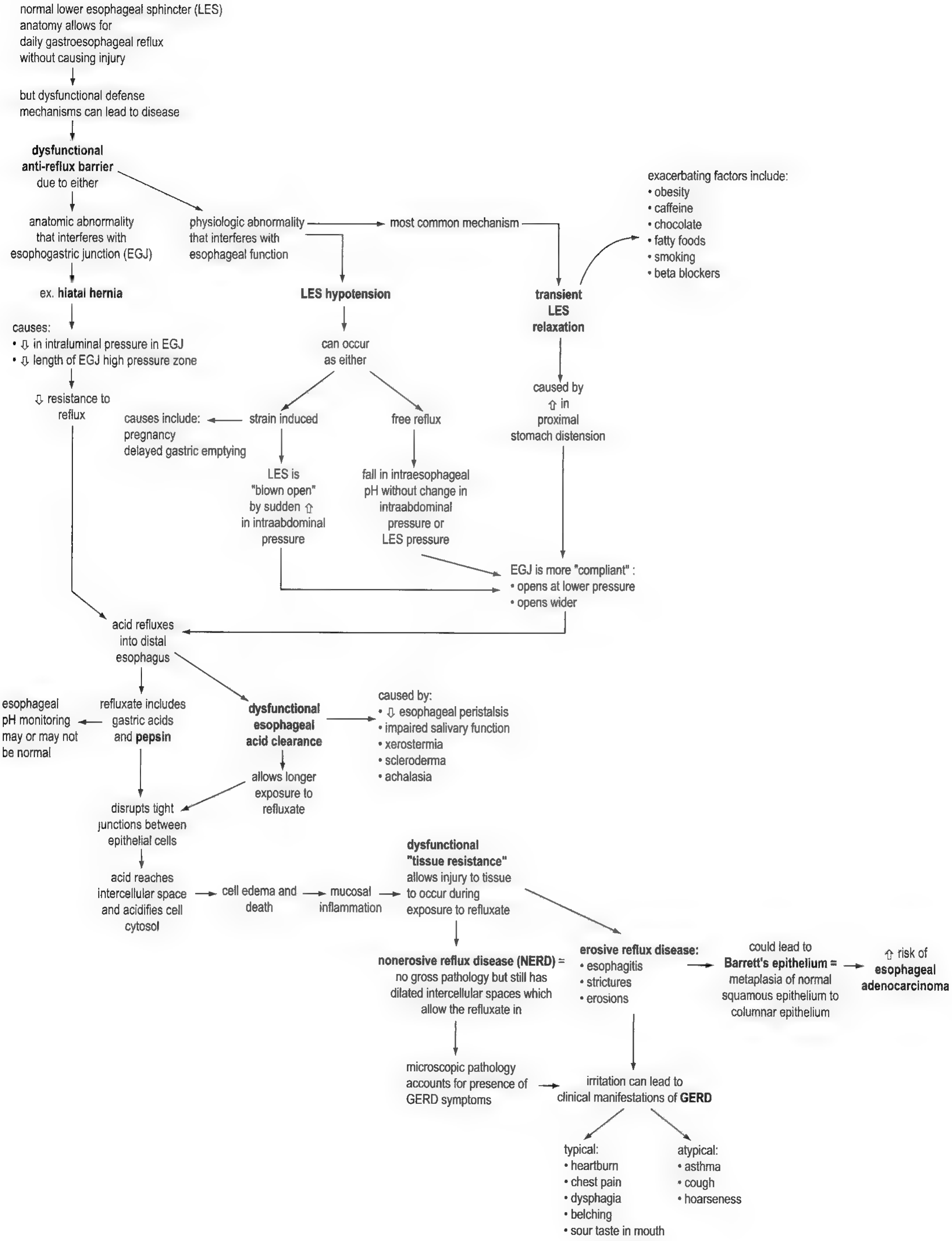
neurologic effects due to ineffective myelination:
- dementia
- delirium
- myelopathy
- gait dysfunction
- paresthesias

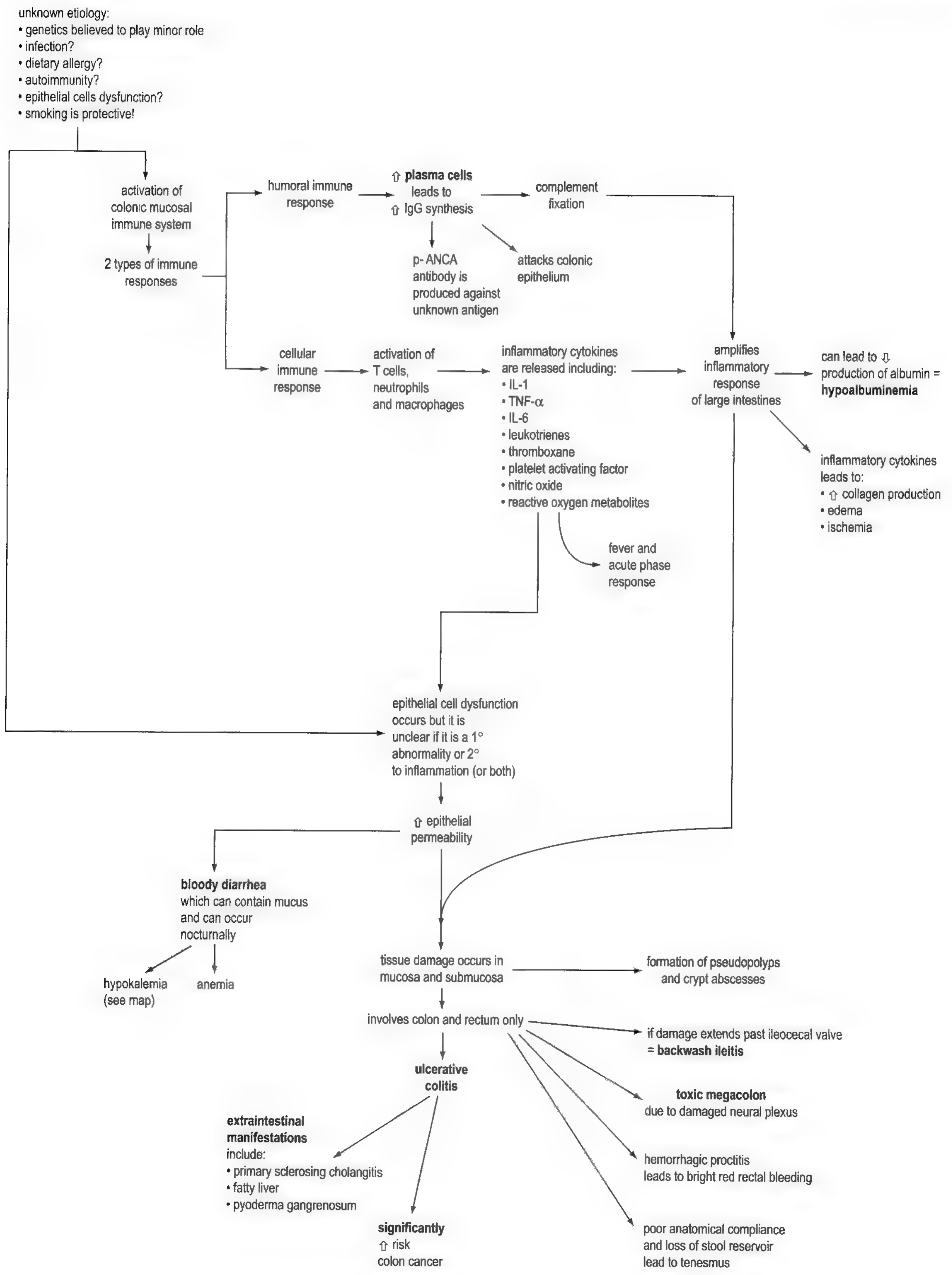
other effects:
- glossitis

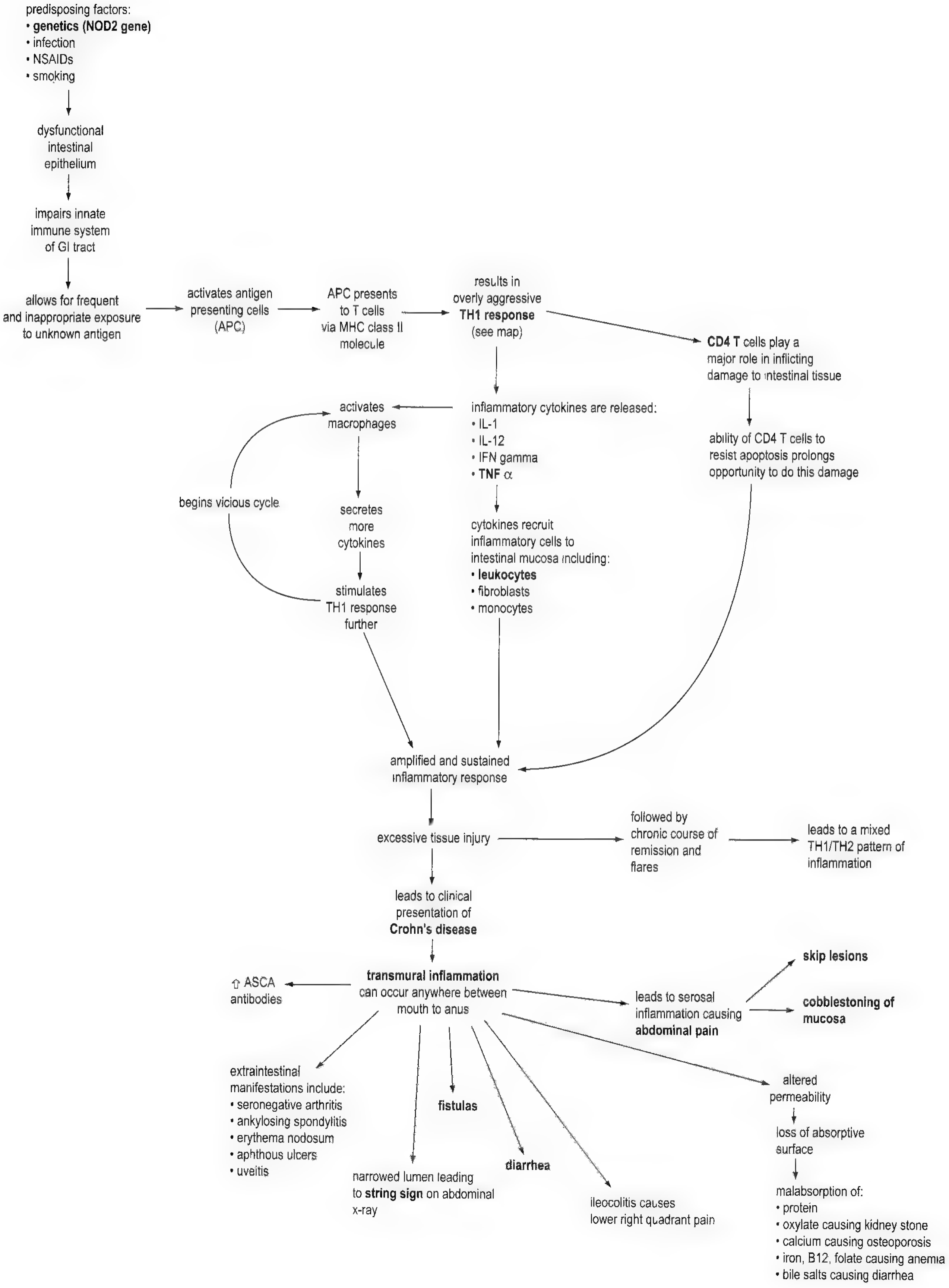

plasma iron pool
supplied by 2 routes of acquisition
1. intestinal absorption
tightly controlled by hepcidin = hormone made by liver
negative regulator of intestinal iron absorption and iron release by RES macrophages
⇧ hepcidin = ⇩ iron absorption and release
⇩ in hepcidin = ⇧ iron absorption and release
iron absorbed by enterocytes has 1 of 2 fates
some iron stored as ferritin within hepatocytes and macrophages
sent to plasma bound to transferrin
most of plasma iron is delivered to bone marrow for erythropoiesis
iron is incorporated into new erythrocytes
red blood cells die after 120 days
2. RBC recycling by reticuloendothelial macrophages
supplies majority of plasma iron pool
HFE gene mutation
most common cause of 1° hemochromatosis
2° hemochromatosis
"expanded" plasma iron pool can be acquired via:
• transfusion overload
• hemolytic anemias
• thalassemias (see map)
• chronic liver disease
⇧ serum iron leads to hemochromatosis
⇧ % saturation of transferrin as excess iron must be bound within plasma
⇩ TIBC as more iron fills binding sites on transferrin
⇧ ferritin as excess iron is put into intracellular storage form
excess iron is deposited as hemosiderin into tissues
causes organ damage
classic triad of hemachromatosis = cirrhosis, bronzed skin, diabetes mellitus
skin:
• ⇧ pigmentation causes bronzing
cardiac:
• restrictive cardiomyopathy
• arrhythmias
• CHF (see map)
liver:
• hepatomegaly
• hepatic dysfunction
• cirrhosis (see map)
endocrine:
• hypogonadism
• impotence
• amenorrhea
• gynecomastia
• diabetes mellitus (see map)
joints:
• arthralgias
immune:
• ⇧ risk of infection with listeria, klebsiella and vibrio

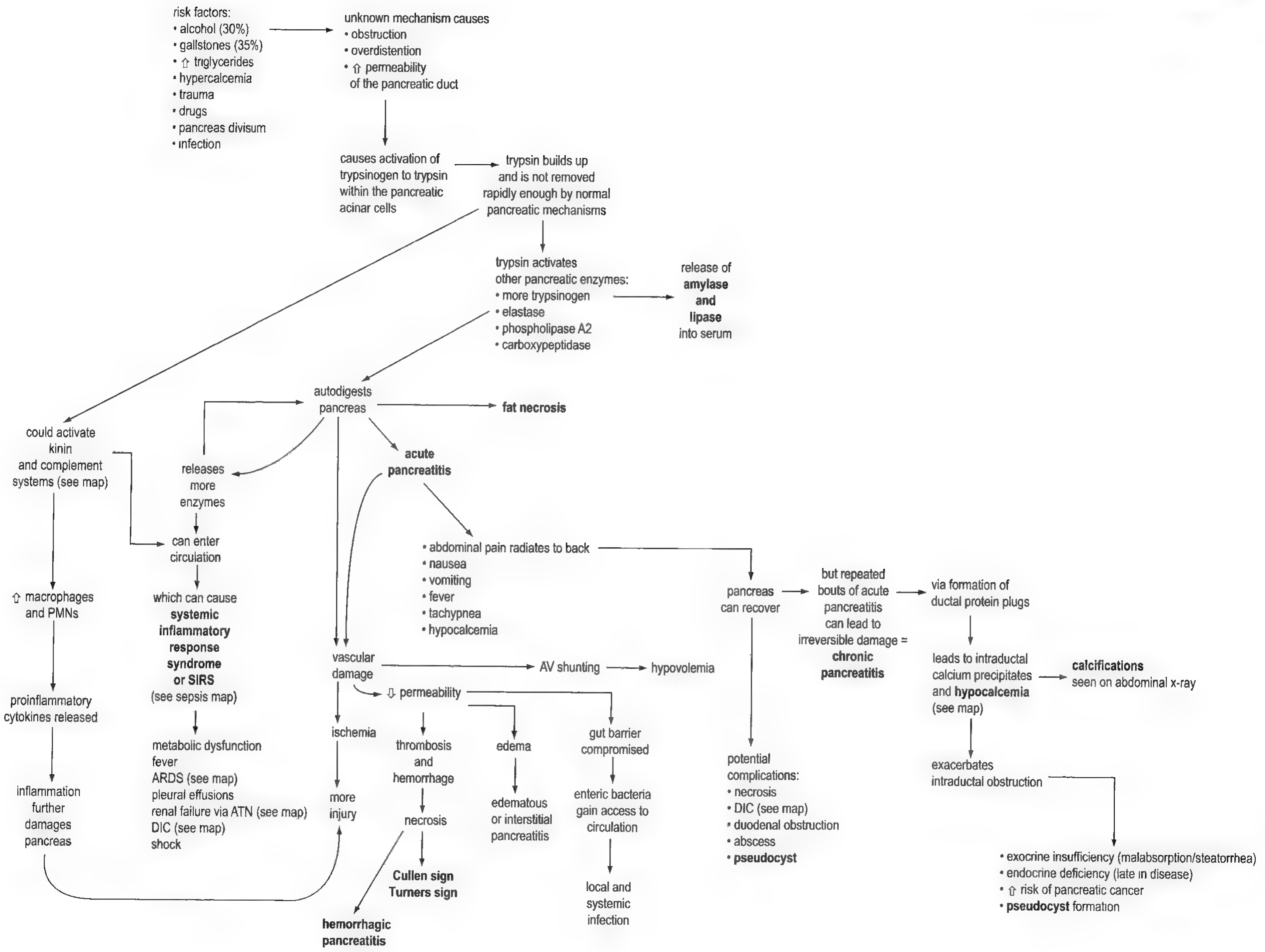

myeloid cell lineage begins with pluripotent hematopoietic stem cells
defect along here can lead to **aplastic anemia**
myeloid stem cell
MP = myeloproliferative
trilineage
megakaryocytes
erythroid
myeloid
MP
MP
MP
essential thrombocytosis
abnormally large platelets
thrombotic or hemorrhagic crisis
myeloid metaplasia with myelosclerosis
splenomegaly due to extramedullary hematopoiesis
acute megakaryocytic leukemia = **M7 AML**
MP
polycythemia vera
M6 AML
⇧ blood volume and viscosity
leads to:
• ulcers
• pruritus
• infarctions
• organ congestion
• DVTs (see map)
• HTN (see map)
hypercellular bone marrow
can go to "spent phase"
leukemic transformation
myelofibrosis
dry bone tap
monoblast
M4 AML
myeloblast
promonocyte
M5 AML
myelodysplasias can progress to
M0 AML
M1 AML
M2 AML
promyelocyte
M3 AML
t(15;17)
contains the most **auer rods**
can lead to DIC (see map)
myelocyte
granulocyte precursors
eosinophilic
basophilic
neutrophilic
MP
chronic myelogenous leukemia (CML)
Philadelphia chromosome (9;22)
bcr-abl fusion gene
⇩ LAP score
can go to **blast crisis**
M2 AML: includes full range of myeloid precursors through granulocytes
auer rods
t(8;12)

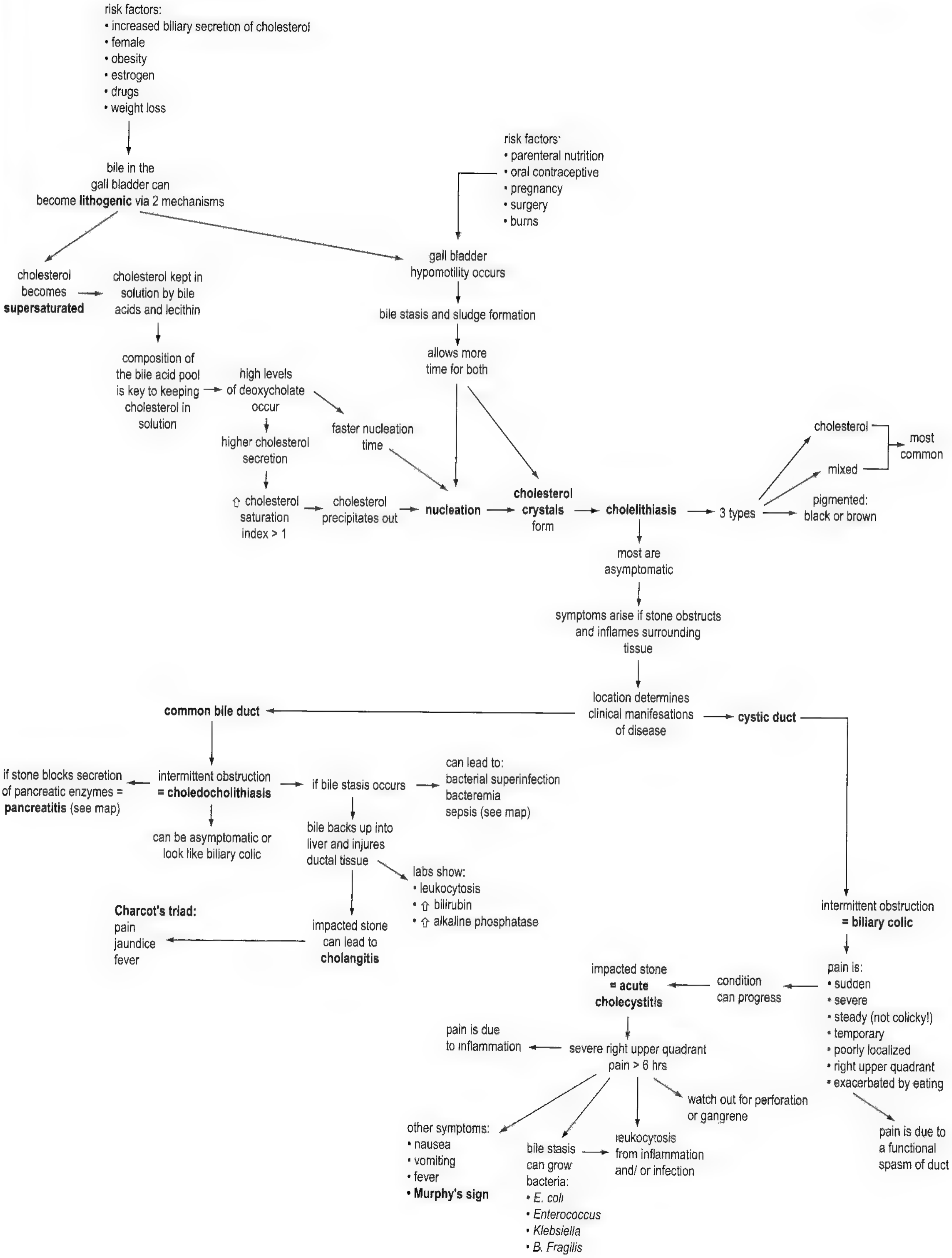

lymphoid cell lineage begins with pluripotent hematopoietic stem cells
lymphoid cells
travel to thymus
become double negative pre-T cell
T cell immunoblast
helper T cell
adult T cell leukemia
cell markers
CD25
CD4
HTLV-1 provirus found in tumor cells
mycosis fungoides
indolent course
plaques develop on skin
progresses to tumors
if malignancy reaches blood = sezary syndrome
travel to bone marrow
common lymphoid precursor
pre-B lymphoblast
naive B cell
acute lymphoblastic leukemia (ALL)
most are pre-B cells but there are 3 types:
• pre-B ALL
• T cell ALL
• B cell ALL
Ig rearrangement occurs
tdt +
small lymphocytic leukemia or chronic lymphocytic leukemia
if abnormal cells found in lymph nodes first = called SLL
CD19
CD20
CD5
cell markers
if abnormal cells found in blood first = called CLL
smudge cells
arrives at lymph nodes
mantle cell
mantle cell lymphoma
t(11;14)
cell markers
CD5
CD19
CD20
germinal center
4 major diseases occur at this stage of B cell development
Non Hodgkin Lymphomas
diffuse large B cell
follicular lymphoma
t(14;18)
small cleaved cells
Burkitts lymphoma
"starry sky"
t(8;14)
Hodgkin lymphoma
characterized by presence of Reed Sternberg cell
malignant cells spread continuously via lymph nodes
use Ann Arbor staging
B symptoms:
• night sweats
• weight loss
painless enlarged lymph nodes
5 WHO subclassifications
nodular sclerosis
lymphocytic predominant
mixed cellularity
lymphocyte depleted
lymphocyte rich
marginal zone
SLL or CLL
marginal zone lymphoma
associated with MALToma
gives rise to either
plasma cells
multiple myeloma
lytic bone lesions
memory B cells
hairy cell leukemia
TRAP +

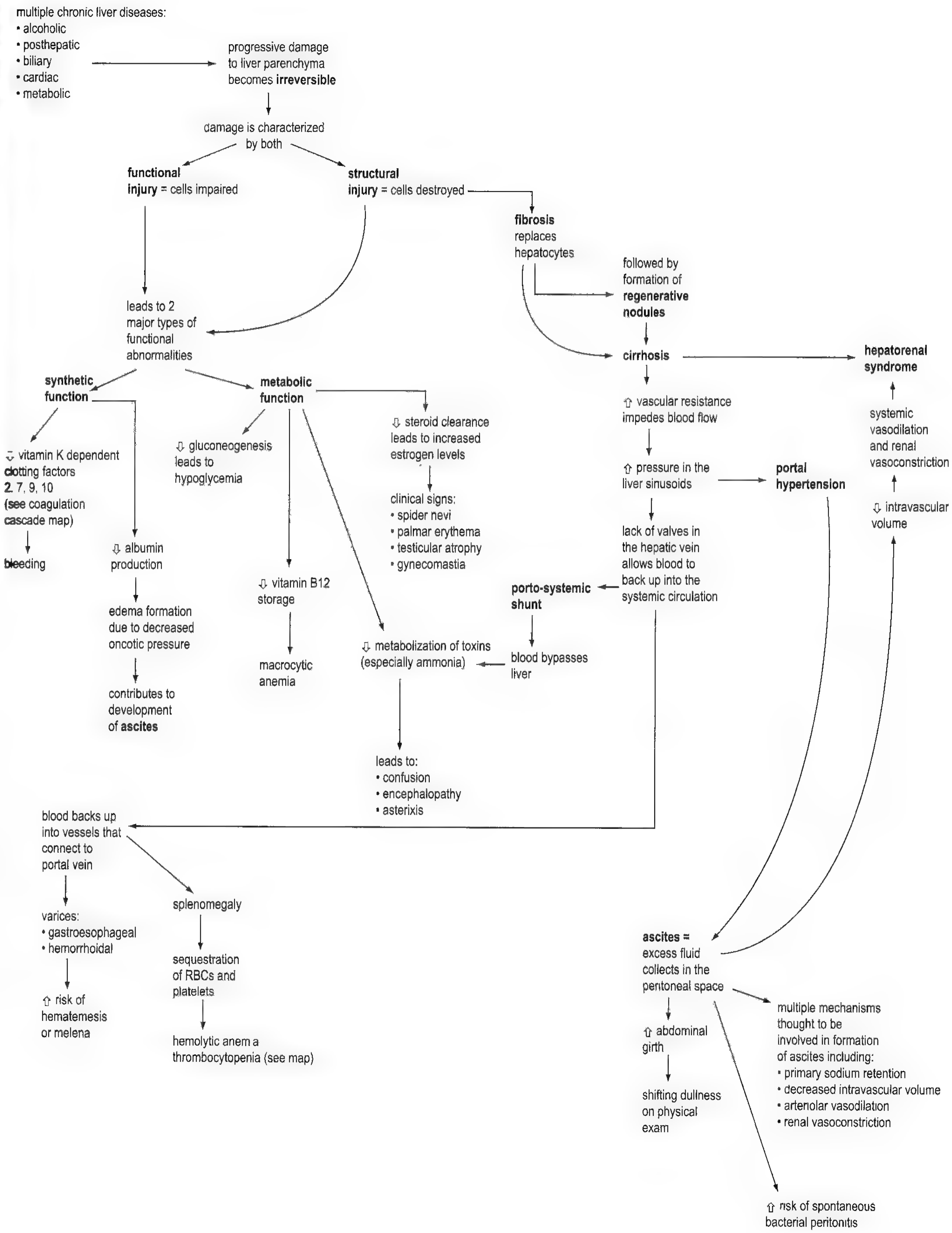

normal lower esophageal sphincter (LES) anatomy allows for daily gastroesophageal reflux without causing injury
but dysfunctional defense mechanisms can lead to disease
dysfunctional anti-reflux barrier due to either
anatomic abnormality that interferes with esophogastric junction (EGJ)
ex. hiatal hernia
causes:
• ⇩ in intraluminal pressure in EGJ
• ⇩ length of EGJ high pressure zone
⇩ resistance to reflux
physiologic abnormality that interferes with esophageal function
most common mechanism
LES hypotension
can occur as either
strain induced
causes include: pregnancy delayed gastric emptying
LES is "blown open" by sudden ⇧ in intraabdominal pressure
free reflux
fall in intraesophageal pH without change in intraabdominal pressure or LES pressure
transient LES relaxation
exacerbating factors include:
• obesity
• caffeine
• chocolate
• fatty foods
• smoking
• beta blockers
caused by ⇧ in proximal stomach distension
EGJ is more "compliant" :
• opens at lower pressure
• opens wider
acid refluxes into distal esophagus
refluxate includes gastric acids and pepsin
esophageal pH monitoring may or may not be normal
dysfunctional esophageal acid clearance
caused by:
• ⇩ esophageal peristalsis
• impaired salivary function
• xerostermia
• scleroderma
• achalasia
allows longer exposure to refluxate
disrupts tight junctions between epithelial cells
acid reaches intercellular space and acidifies cell cytosol
cell edema and death
mucosal inflammation
dysfunctional "tissue resistance" allows injury to tissue to occur during exposure to refluxate
nonerosive reflux disease (NERD) = no gross pathology but still has dilated intercellular spaces which allow the refluxate in
erosive reflux disease:
• esophagitis
• strictures
• erosions
could lead to Barrett's epithelium = metaplasia of normal squamous epithelium to columnar epithelium
⇧ risk of esophageal adenocarcinoma
microscopic pathology accounts for presence of GERD symptoms
irritation can lead to clinical manifestations of GERD
typical:
• heartburn
• chest pain
• dysphagia
• belching
• sour taste in mouth
atypical:
• asthma
• cough
• hoarseness

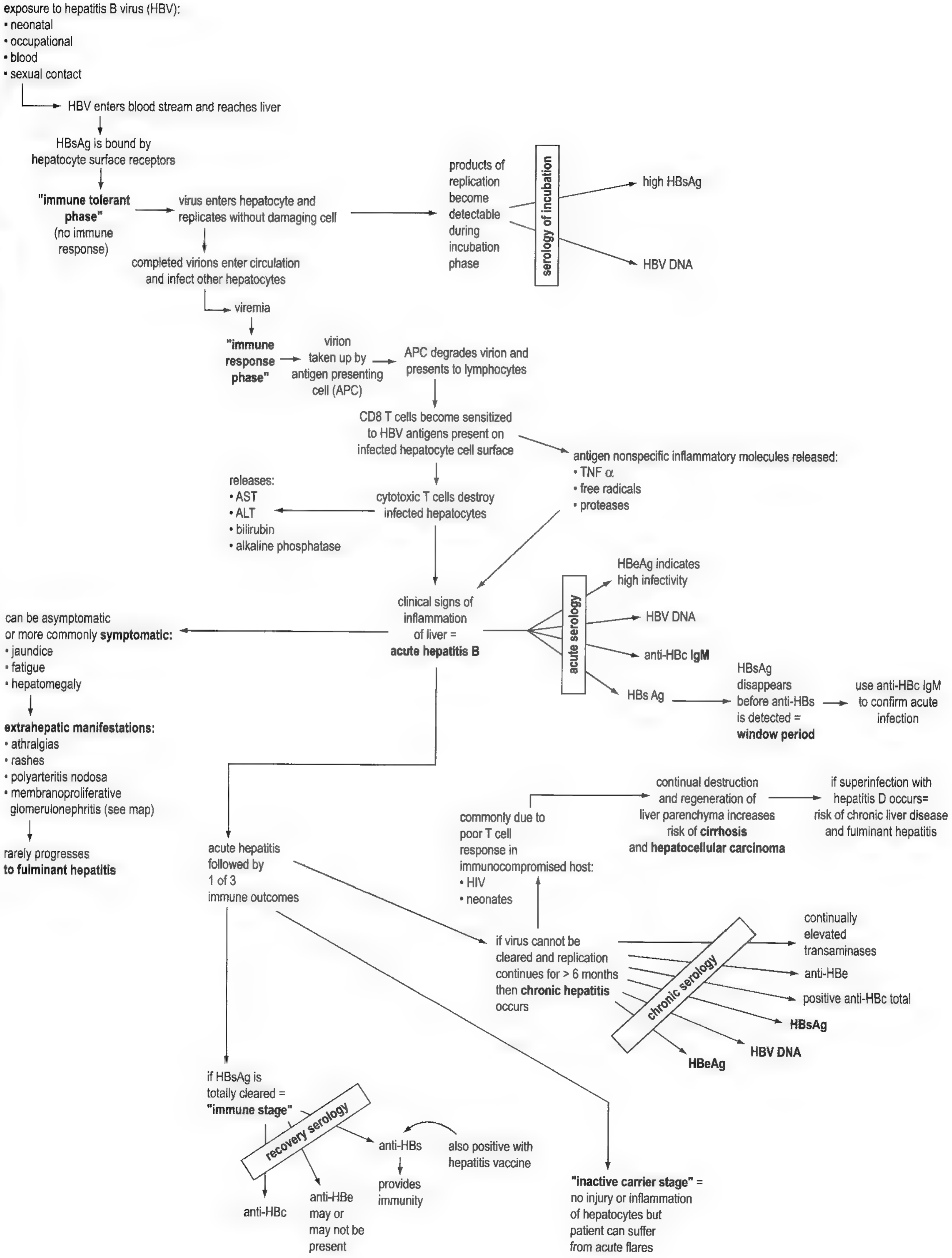

unknown etiology:
• genetics believed to play minor role
• infection?
• dietary allergy?
• autoimmunity?
• epithelial cells dysfunction?
• smoking is protective!
activation of colonic mucosal immune system
2 types of immune responses
humoral immune response
⇧ **plasma cells** leads to ⇧ IgG synthesis
complement fixation
p-ANCA antibody is produced against unknown antigen
attacks colonic epithelium
cellular immune response
activation of T cells, neutrophils and macrophages
inflammatory cytokines are released including:
• IL-1
• TNF-α
• IL-6
• leukotrienes
• thromboxane
• platelet activating factor
• nitric oxide
• reactive oxygen metabolites
amplifies inflammatory response of large intestines
can lead to ⇩ production of albumin = **hypoalbuminemia**
inflammatory cytokines leads to:
• ⇧ collagen production
• edema
• ischemia
fever and acute phase response
epithelial cell dysfunction occurs but it is unclear if it is a 1° abnormality or 2° to inflammation (or both)
⇧ epithelial permeability
bloody diarrhea which can contain mucus and can occur nocturnally
hypokalemia (see map)
anemia
tissue damage occurs in mucosa and submucosa
formation of pseudopolyps and crypt abscesses
involves colon and rectum only
if damage extends past ileocecal valve = **backwash ileitis**
ulcerative colitis
toxic megacolon due to damaged neural plexus
extraintestinal manifestations include:
• primary sclerosing cholangitis
• fatty liver
• pyoderma gangrenosum
hemorrhagic proctitis leads to bright red rectal bleeding
significantly ⇧ risk colon cancer
poor anatomical compliance and loss of stool reservoir lead to tenesmus


predisposing factors:
• **genetics (NOD2 gene)**
• infection
• NSAIDs
• smoking
dysfunctional intestinal epithelium
impairs innate immune system of GI tract
allows for frequent and inappropriate exposure to unknown antigen
activates antigen presenting cells (APC)
APC presents to T cells via MHC class II molecule
results in overly aggressive **TH1 response** (see map)
CD4 T cells play a major role in inflicting damage to intestinal tissue
ability of CD4 T cells to resist apoptosis prolongs opportunity to do this damage
inflammatory cytokines are released:
• IL-1
• IL-12
• IFN gamma
• **TNF α**
activates macrophages
begins vicious cycle
secretes more cytokines
stimulates TH1 response further
cytokines recruit inflammatory cells to intestinal mucosa including:
• **leukocytes**
• fibroblasts
• monocytes
amplified and sustained inflammatory response
excessive tissue injury
followed by chronic course of remission and flares
leads to a mixed TH1/TH2 pattern of inflammation
leads to clinical presentation of **Crohn's disease**
transmural inflammation can occur anywhere between mouth to anus
⇧ ASCA antibodies
leads to serosal inflammation causing **abdominal pain**
skip lesions
cobblestoning of mucosa
extraintestinal manifestations include:
• seronegative arthritis
• ankylosing spondylitis
• erythema nodosum
• aphthous ulcers
• uveitis
fistulas
narrowed lumen leading to **string sign** on abdominal x-ray
diarrhea
ileocolitis causes lower right quadrant pain
altered permeability
loss of absorptive surface
malabsorption of:
• protein
• oxylate causing kidney stone
• calcium causing osteoporosis
• iron, B12, folate causing anemia
• bile salts causing diarrhea


risk factors:
• alcohol (30%)
• gallstones (35%)
• ⇧ triglycerides
• hypercalcemia
• trauma
• drugs
• pancreas divisum
• infection
unknown mechanism causes
• obstruction
• overdistention
• ⇧ permeability of the pancreatic duct
causes activation of trypsinogen to trypsin within the pancreatic acinar cells
trypsin builds up and is not removed rapidly enough by normal pancreatic mechanisms
trypsin activates other pancreatic enzymes:
• more trypsinogen
• elastase
• phospholipase A2
• carboxypeptidase
release of **amylase and lipase** into serum
could activate kinin and complement systems (see map)
⇧ macrophages and PMNs
proinflammatory cytokines released
inflammation further damages pancreas
autodigests pancreas
fat necrosis
releases more enzymes
can enter circulation
which can cause **systemic inflammatory response syndrome or SIRS** (see sepsis map)
metabolic dysfunction
fever
ARDS (see map)
pleural effusions
renal failure via ATN (see map)
DIC (see map)
shock
acute pancreatitis
• abdominal pain radiates to back
• nausea
• vomiting
• fever
• tachypnea
• hypocalcemia
vascular damage
AV shunting
hypovolemia
⇩ permeability
ischemia
more injury
thrombosis and hemorrhage
necrosis
Cullen sign
Turners sign
hemorrhagic pancreatitis
edema
edematous or interstitial pancreatitis
gut barrier compromised
enteric bacteria gain access to circulation
local and systemic infection
pancreas can recover
potential complications:
• necrosis
• DIC (see map)
• duodenal obstruction
• abscess
• **pseudocyst**
but repeated bouts of acute pancreatitis can lead to irreversible damage = **chronic pancreatitis**
via formation of ductal protein plugs
leads to intraductal calcium precipitates and **hypocalcemia** (see map)
calcifications seen on abdominal x-ray
exacerbates intraductal obstruction
• exocrine insufficiency (malabsorption/steatorrhea)
• endocrine deficiency (late in disease)
• ⇧ risk of pancreatic cancer
• **pseudocyst** formation


risk factors:
• increased biliary secretion of cholesterol
• female
• obesity
• estrogen
• drugs
• weight loss
bile in the gall bladder can become **lithogenic** via 2 mechanisms
risk factors:
• parenteral nutrition
• oral contraceptive
• pregnancy
• surgery
• burns
cholesterol becomes **supersaturated**
cholesterol kept in solution by bile acids and lecithin
gall bladder hypomotility occurs
bile stasis and sludge formation
allows more time for both
composition of the bile acid pool is key to keeping cholesterol in solution
high levels of deoxycholate occur
faster nucleation time
higher cholesterol secretion
⇧ cholesterol saturation index > 1
cholesterol precipitates out
nucleation
cholesterol crystals form
cholelithiasis
3 types
cholesterol
mixed
most common
pigmented: black or brown
most are asymptomatic
symptoms arise if stone obstructs and inflames surrounding tissue
location determines clinical manifesations of disease
common bile duct
cystic duct
if stone blocks secretion of pancreatic enzymes = **pancreatitis** (see map)
intermittent obstruction **= choledocholithiasis**
if bile stasis occurs
can lead to: bacterial superinfection bacteremia sepsis (see map)
can be asymptomatic or look like biliary colic
bile backs up into liver and injures ductal tissue
labs show:
• leukocytosis
• ⇧ bilirubin
• ⇧ alkaline phosphatase
Charcot's triad: pain jaundice fever
impacted stone can lead to **cholangitis**
intermittent obstruction **= biliary colic**
pain is:
• sudden
• severe
• steady (not colicky!)
• temporary
• poorly localized
• right upper quadrant
• exacerbated by eating
condition can progress
impacted stone **= acute cholecystitis**
pain is due to inflammation
severe right upper quadrant pain > 6 hrs
watch out for perforation or gangrene
pain is due to a functional spasm of duct
other symptoms:
• nausea
• vomiting
• fever
• **Murphy's sign**
bile stasis can grow bacteria:
• *E. coli*
• *Enterococcus*
• *Klebsiella*
• *B. Fragilis*
leukocytosis from inflammation and/ or infection


multiple chronic liver diseases:
• alcoholic
• posthepatic
• biliary
• cardiac
• metabolic
progressive damage to liver parenchyma becomes **irreversible**
damage is characterized by both
functional injury = cells impaired
structural injury = cells destroyed
fibrosis replaces hepatocytes
followed by formation of **regenerative nodules**
cirrhosis
hepatorenal syndrome
leads to 2 major types of functional abnormalities
synthetic function
metabolic function
⇩ vitamin K dependent clotting factors 2, 7, 9, 10 (see coagulation cascade map)
bleeding
⇩ albumin production
edema formation due to decreased oncotic pressure
contributes to development of **ascites**
⇩ gluconeogenesis leads to hypoglycemia
⇩ vitamin B12 storage
macrocytic anemia
⇩ steroid clearance leads to increased estrogen levels
clinical signs:
• spider nevi
• palmar erythema
• testicular atrophy
• gynecomastia
⇩ metabolization of toxins (especially ammonia)
leads to:
• confusion
• encephalopathy
• asterixis
⇧ vascular resistance impedes blood flow
⇧ pressure in the liver sinusoids
portal hypertension
lack of valves in the hepatic vein allows blood to back up into the systemic circulation
porto-systemic shunt
blood bypasses liver
systemic vasodilation and renal vasoconstriction
⇩ intravascular volume
blood backs up into vessels that connect to portal vein
varices:
• gastroesophageal
• hemorrhoidal
⇧ risk of hematemesis or melena
splenomegaly
sequestration of RBCs and platelets
hemolytic anemia thrombocytopenia (see map)
ascites = excess fluid collects in the peritoneal space
⇧ abdominal girth
shifting dullness on physical exam
multiple mechanisms thought to be involved in formation of ascites including:
• primary sodium retention
• decreased intravascular volume
• arteriolar vasodilation
• renal vasoconstriction
⇧ risk of spontaneous bacterial peritonitis



exposure to hepatitis B virus (HBV):
- neonatal
- occupational
- blood
- sexual contact

HBV enters blood stream and reaches liver

HBsAg is bound by hepatocyte surface receptors

"immune tolerant phase" (no immune response)

virus enters hepatocyte and replicates without damaging cell

products of replication become detectable during incubation phase

serology of incubation

high HBsAg

HBV DNA

completed virions enter circulation and infect other hepatocytes

viremia

"immune response phase"

virion taken up by antigen presenting cell (APC)

APC degrades virion and presents to lymphocytes

CD8 T cells become sensitized to HBV antigens present on infected hepatocyte cell surface

antigen nonspecific inflammatory molecules released:
- TNF α
- free radicals
- proteases

cytotoxic T cells destroy infected hepatocytes

releases:
- AST
- ALT
- bilirubin
- alkaline phosphatase

clinical signs of inflammation of liver = **acute hepatitis B**

can be asymptomatic or more commonly **symptomatic:**
- jaundice
- fatigue
- hepatomegaly

extrahepatic manifestations:
- athralgias
- rashes
- polyarteritis nodosa
- membranoproliferative glomerulonephritis (see map)

rarely progresses **to fulminant hepatitis**

acute serology

HBeAg indicates high infectivity

HBV DNA

anti-HBc **IgM**

HBs Ag

HBsAg disappears before anti-HBs is detected = **window period**

use anti-HBc IgM to confirm acute infection

acute hepatitis followed by 1 of 3 immune outcomes

if virus cannot be cleared and replication continues for > 6 months then **chronic hepatitis** occurs

commonly due to poor T cell response in immunocompromised host:
- HIV
- neonates

continual destruction and regeneration of liver parenchyma increases risk of **cirrhosis** and **hepatocellular carcinoma**

if superinfection with hepatitis D occurs= risk of chronic liver disease and fulminant hepatitis

chronic serology

continually elevated transaminases

anti-HBe

positive anti-HBc total

HBsAg

HBV DNA

HBeAg

if HBsAg is totally cleared = **"immune stage"**

recovery serology

anti-HBc

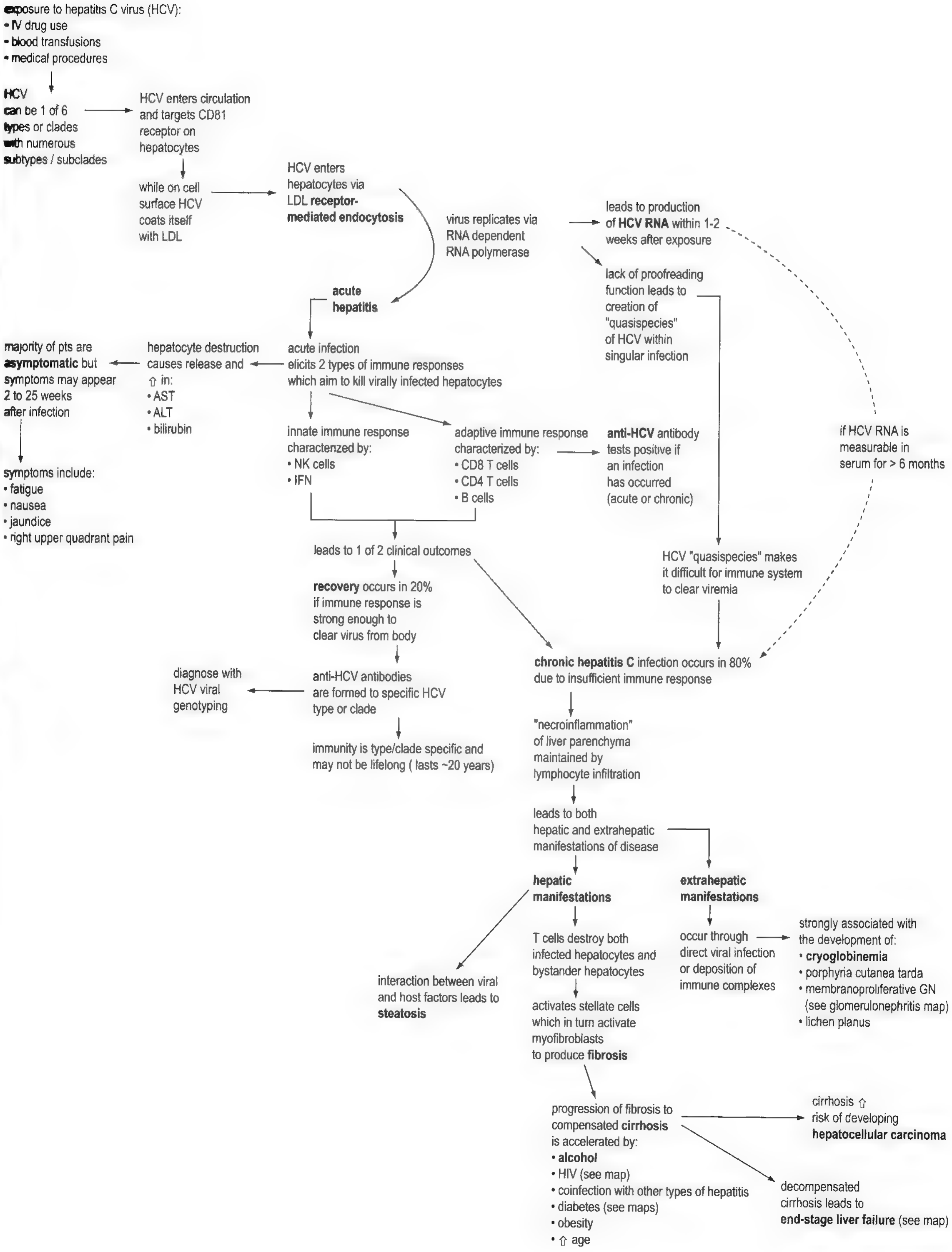
anti-HBe may or may not be present

anti-HBs

provides immunity

also positive with hepatitis vaccine

"inactive carrier stage" = no injury or inflammation of hepatocytes but patient can suffer from acute flares



exposure to hepatitis C virus (HCV):
- IV drug use
- blood transfusions
- medical procedures

HCV can be 1 of 6 types or clades with numerous subtypes / subclades

HCV enters circulation and targets CD81 receptor on hepatocytes

while on cell surface HCV coats itself with LDL

HCV enters hepatocytes via LDL **receptor-mediated endocytosis**

virus replicates via RNA dependent RNA polymerase

leads to production of **HCV RNA** within 1-2 weeks after exposure

lack of proofreading function leads to creation of "quasispecies" of HCV within singular infection

acute hepatitis

acute infection elicits 2 types of immune responses which aim to kill virally infected hepatocytes

hepatocyte destruction causes release and ⇧ in:
- AST
- ALT
- bilirubin

majority of pts are **asymptomatic** but symptoms may appear 2 to 25 weeks after infection

symptoms include:
- fatigue
- nausea
- jaundice
- right upper quadrant pain

innate immune response characterized by:
- NK cells
- IFN

adaptive immune response characterized by:
- CD8 T cells
- CD4 T cells
- B cells

anti-HCV antibody tests positive if an infection has occurred (acute or chronic)

leads to 1 of 2 clinical outcomes

recovery occurs in 20% if immune response is strong enough to clear virus from body

anti-HCV antibodies are formed to specific HCV type or clade

diagnose with HCV viral genotyping

immunity is type/clade specific and may not be lifelong (lasts ~20 years)

HCV "quasispecies" makes it difficult for immune system to clear viremia

if HCV RNA is measurable in serum for > 6 months

chronic hepatitis C infection occurs in 80% due to insufficient immune response

"necroinflammation" of liver parenchyma maintained by lymphocyte infiltration

leads to both hepatic and extrahepatic manifestations of disease

hepatic manifestations

interaction between viral and host factors leads to **steatosis**

T cells destroy both infected hepatocytes and bystander hepatocytes

activates stellate cells which in turn activate myofibroblasts to produce **fibrosis**

progression of fibrosis to compensated **cirrhosis** is accelerated by:
- **alcohol**
- HIV (see map)
- coinfection with other types of hepatitis
- diabetes (see maps)
- obesity
- ⇧ age

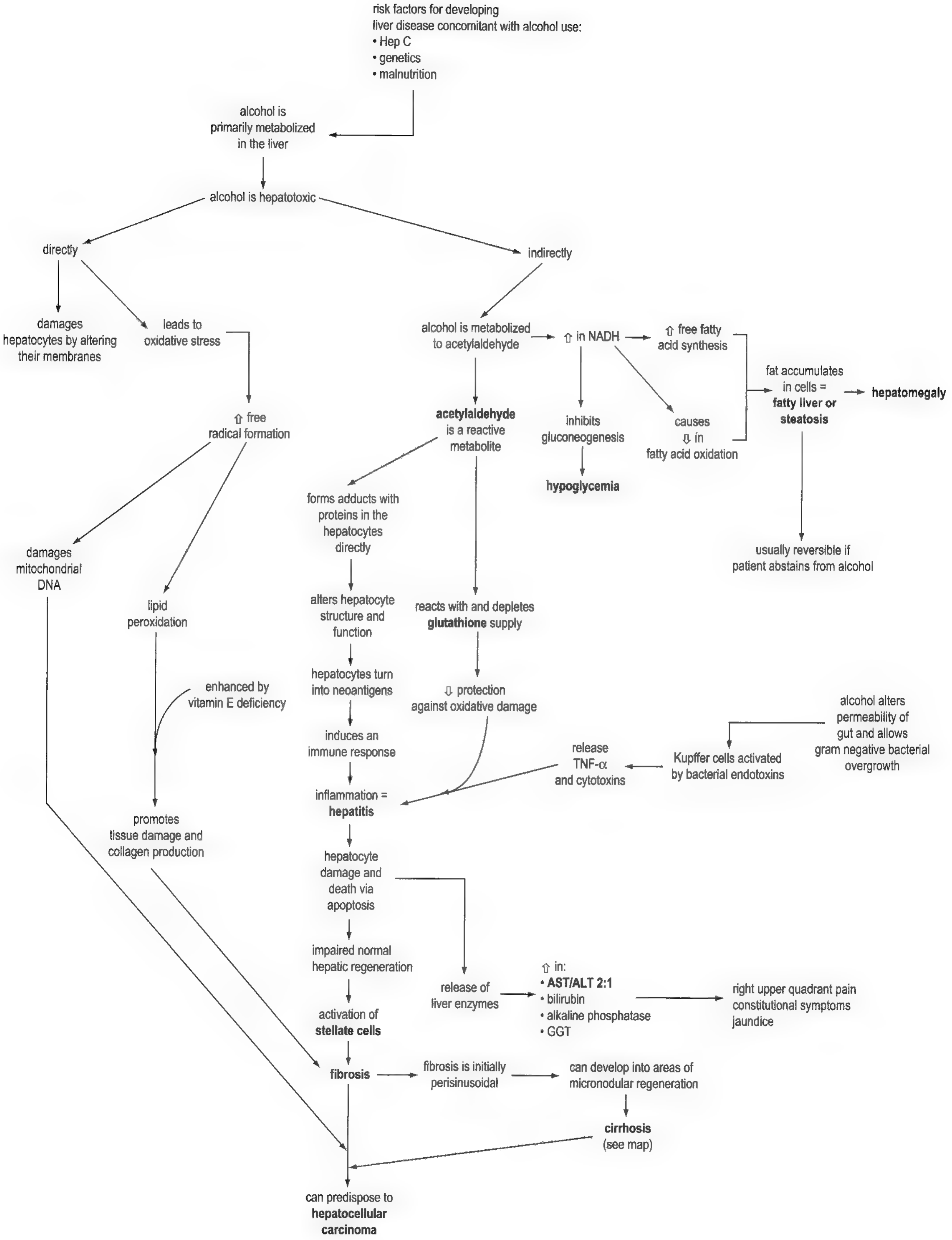
cirrhosis ⇧ risk of developing **hepatocellular carcinoma**

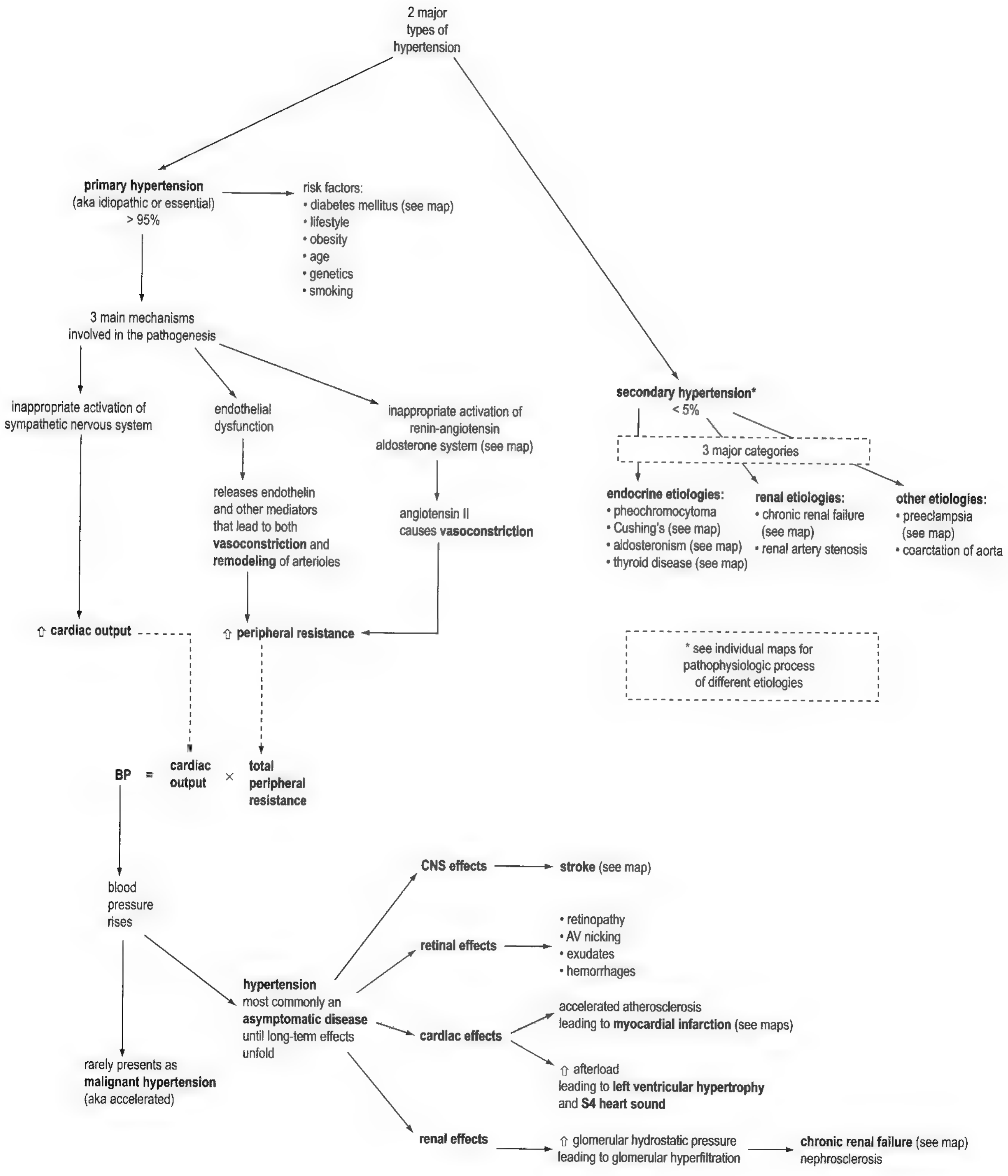
decompensated cirrhosis leads to **end-stage liver failure** (see map)

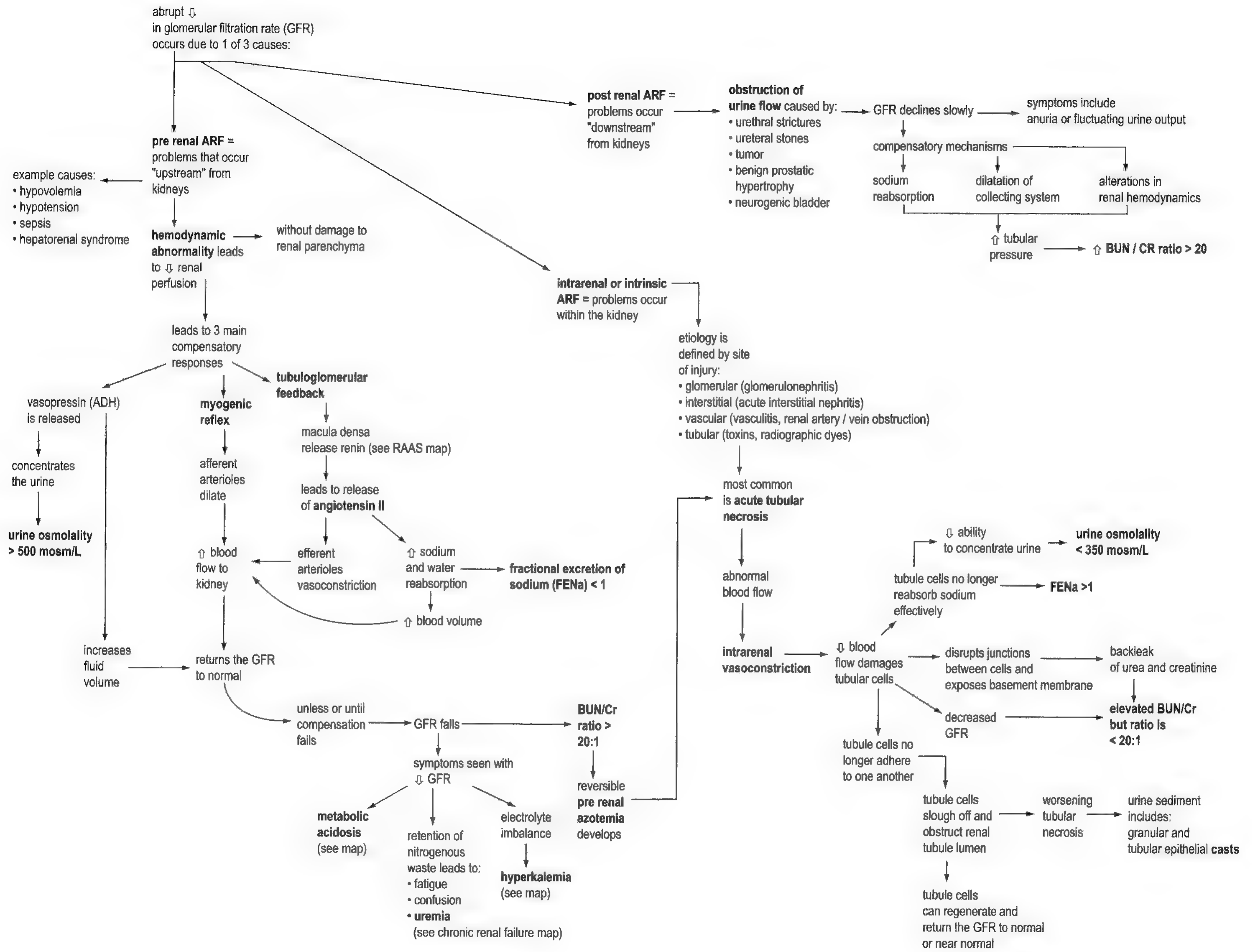
extrahepatic manifestations

occur through direct viral infection or deposition of immune complexes

strongly associated with the development of:
- **cryoglobinemia**
- porphyria cutanea tarda
- membranoproliferative GN (see glomerulonephritis map)
- lichen planus


risk factors for developing liver disease concomitant with alcohol use:
• Hep C
• genetics
• malnutrition
alcohol is primarily metabolized in the liver
alcohol is hepatotoxic
directly
indirectly
damages hepatocytes by altering their membranes
leads to oxidative stress
⇧ free radical formation
damages mitochondrial DNA
lipid peroxidation
enhanced by vitamin E deficiency
promotes tissue damage and collagen production
alcohol is metabolized to acetylaldehyde
⇧ in NADH
⇧ free fatty acid synthesis
inhibits gluconeogenesis
hypoglycemia
causes ⇩ in fatty acid oxidation
fat accumulates in cells = fatty liver or steatosis
hepatomegaly
usually reversible if patient abstains from alcohol
acetylaldehyde is a reactive metabolite
forms adducts with proteins in the hepatocytes directly
alters hepatocyte structure and function
hepatocytes turn into neoantigens
induces an immune response
reacts with and depletes glutathione supply
⇩ protection against oxidative damage
alcohol alters permeability of gut and allows gram negative bacterial overgrowth
Kupffer cells activated by bacterial endotoxins
release TNF-α and cytotoxins
inflammation = hepatitis
hepatocyte damage and death via apoptosis
impaired normal hepatic regeneration
activation of stellate cells
release of liver enzymes
⇧ in:
• AST/ALT 2:1
• bilirubin
• alkaline phosphatase
• GGT
right upper quadrant pain
constitutional symptoms
jaundice
fibrosis
fibrosis is initially perisinusoidal
can develop into areas of micronodular regeneration
cirrhosis (see map)
can predispose to hepatocellular carcinoma


2 major types of hypertension
primary hypertension (aka idiopathic or essential) > 95%
risk factors:
• diabetes mellitus (see map)
• lifestyle
• obesity
• age
• genetics
• smoking
3 main mechanisms involved in the pathogenesis
inappropriate activation of sympathetic nervous system
endothelial dysfunction
inappropriate activation of renin-angiotensin aldosterone system (see map)
releases endothelin and other mediators that lead to both vasoconstriction and remodeling of arterioles
angiotensin II causes vasoconstriction
⇧ cardiac output
⇧ peripheral resistance
BP = cardiac output × total peripheral resistance
blood pressure rises
rarely presents as malignant hypertension (aka accelerated)
hypertension most commonly an asymptomatic disease until long-term effects unfold
CNS effects
stroke (see map)
retinal effects
• retinopathy
• AV nicking
• exudates
• hemorrhages
cardiac effects
accelerated atherosclerosis leading to myocardial infarction (see maps)
⇧ afterload leading to left ventricular hypertrophy and S4 heart sound
renal effects
⇧ glomerular hydrostatic pressure leading to glomerular hyperfiltration
chronic renal failure (see map) nephrosclerosis
secondary hypertension* < 5%
3 major categories
endocrine etiologies:
• pheochromocytoma
• Cushing's (see map)
• aldosteronism (see map)
• thyroid disease (see map)
renal etiologies:
• chronic renal failure (see map)
• renal artery stenosis
other etiologies:
• preeclampsia (see map)
• coarctation of aorta
* see individual maps for pathophysiologic process of different etiologies



abrupt ⇩ in glomerular filtration rate (GFR) occurs due to 1 of 3 causes:

pre renal ARF = problems that occur "upstream" from kidneys

example causes:
- hypovolemia
- hypotension
- sepsis
- hepatorenal syndrome

hemodynamic abnormality leads to ⇩ renal perfusion → without damage to renal parenchyma

leads to 3 main compensatory responses

vasopressin (ADH) is released → concentrates the urine → **urine osmolality > 500 mosm/L**

vasopressin (ADH) is released → increases fluid volume → returns the GFR to normal

myogenic reflex → afferent arterioles dilate → ⇧ blood flow to kidney → returns the GFR to normal

tubuloglomerular feedback → macula densa release renin (see RAAS map) → leads to release of **angiotensin II**

angiotensin II → efferent arterioles vasoconstriction → ⇧ blood flow to kidney

angiotensin II → ⇧ sodium and water reabsorption → **fractional excretion of sodium (FENa) < 1**

⇧ sodium and water reabsorption → ⇧ blood volume → ⇧ blood flow to kidney

returns the GFR to normal → unless or until compensation fails → GFR falls → **BUN/Cr ratio > 20:1** → reversible **pre renal azotemia** develops → most common is **acute tubular necrosis**

GFR falls → symptoms seen with ⇩ GFR:
- **metabolic acidosis** (see map)
- retention of nitrogenous waste leads to:
  - fatigue
  - confusion
  - **uremia** (see chronic renal failure map)
- electrolyte imbalance → **hyperkalemia** (see map)

post renal ARF = problems occur "downstream" from kidneys

obstruction of urine flow caused by:
- urethral strictures
- ureteral stones
- tumor
- benign prostatic hypertrophy
- neurogenic bladder

→ GFR declines slowly → symptoms include anuria or fluctuating urine output

GFR declines slowly → compensatory mechanisms → sodium reabsorption / dilatation of collecting system / alterations in renal hemodynamics → ⇧ tubular pressure → ⇧ **BUN / CR ratio > 20**

intrarenal or intrinsic ARF = problems occur within the kidney

etiology is defined by site of injury:
- glomerular (glomerulonephritis)
- interstitial (acute interstitial nephritis)
- vascular (vasculitis, renal artery / vein obstruction)
- tubular (toxins, radiographic dyes)

→ most common is **acute tubular necrosis** → abnormal blood flow → **intrarenal vasoconstriction** → ⇩ blood flow damages tubular cells

⇩ blood flow damages tubular cells → tubule cells no longer reabsorb sodium effectively → FENa >1

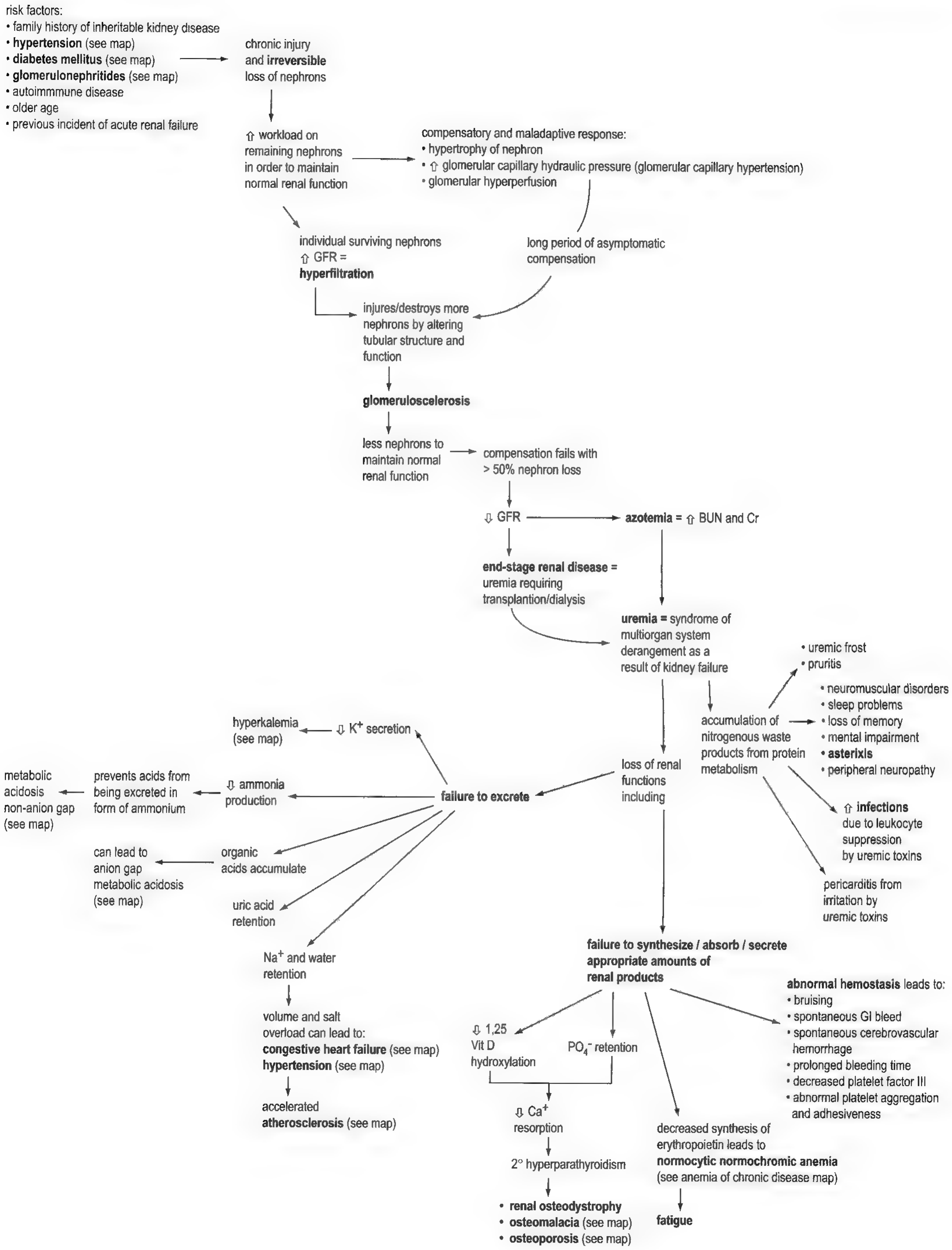
tubule cells no longer reabsorb sodium effectively → ⇩ ability to concentrate urine → **urine osmolality < 350 mosm/L**

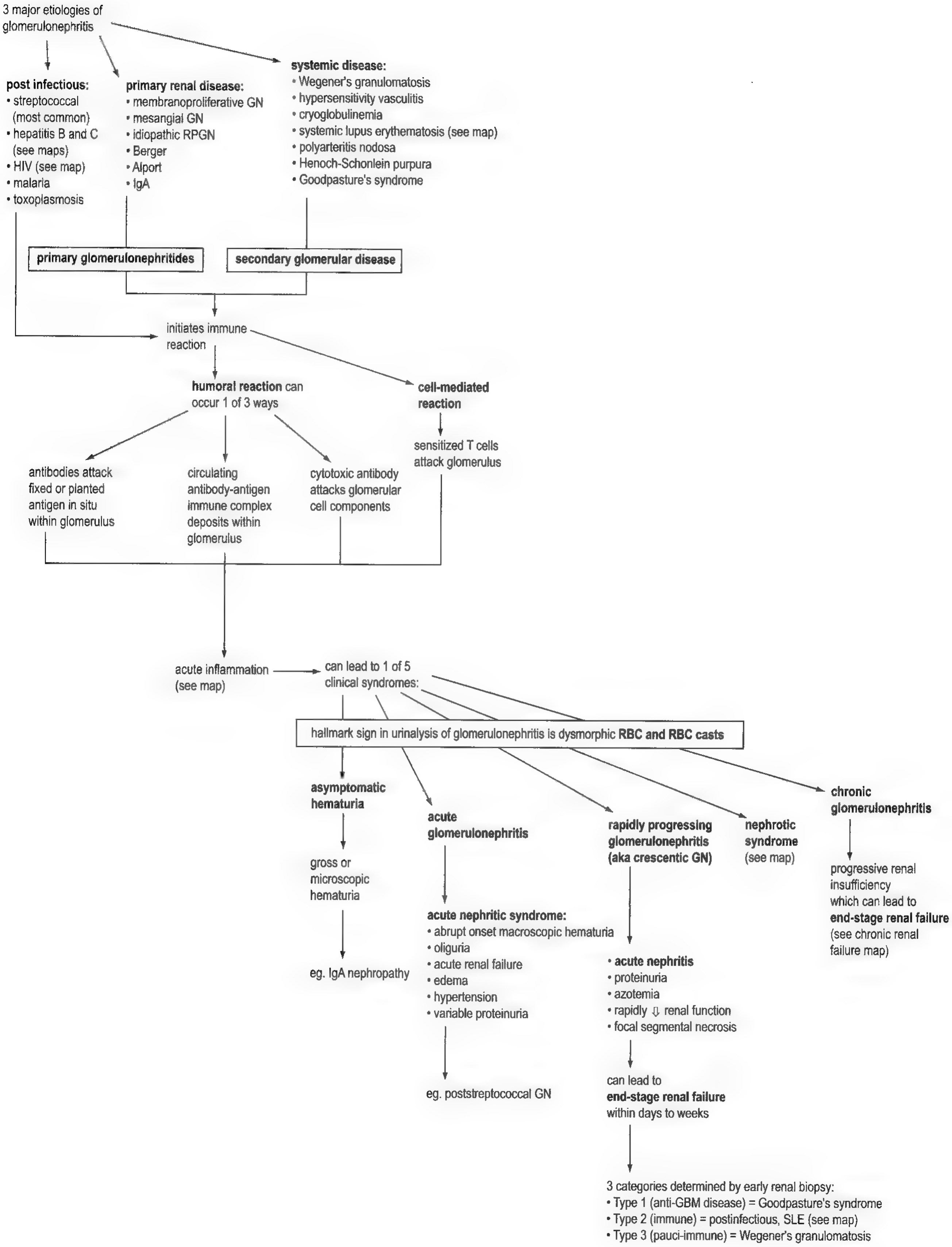
⇩ blood flow damages tubular cells → disrupts junctions between cells and exposes basement membrane → backleak of urea and creatinine → **elevated BUN/Cr but ratio is < 20:1**

⇩ blood flow damages tubular cells → decreased GFR → **elevated BUN/Cr but ratio is < 20:1**

⇩ blood flow damages tubular cells → tubule cells no longer adhere to one another → tubule cells slough off and obstruct renal tubule lumen → worsening tubular necrosis → urine sediment includes: granular and tubular epithelial **casts**

tubule cells slough off and obstruct renal tubule lumen → tubule cells can regenerate and return the GFR to normal or near normal


risk factors:
• family history of inheritable kidney disease
• hypertension (see map)
• diabetes mellitus (see map)
• glomerulonephritides (see map)
• autoimmmune disease
• older age
• previous incident of acute renal failure
chronic injury and irreversible loss of nephrons
⇧ workload on remaining nephrons in order to maintain normal renal function
compensatory and maladaptive response:
• hypertrophy of nephron
• ⇧ glomerular capillary hydraulic pressure (glomerular capillary hypertension)
• glomerular hyperperfusion
individual surviving nephrons ⇧ GFR = hyperfiltration
long period of asymptomatic compensation
injures/destroys more nephrons by altering tubular structure and function
glomerulosclerosis
less nephrons to maintain normal renal function
compensation fails with > 50% nephron loss
⇩ GFR
azotemia = ⇧ BUN and Cr
end-stage renal disease = uremia requiring transplantion/dialysis
uremia = syndrome of multiorgan system derangement as a result of kidney failure
• uremic frost
• pruritis
• neuromuscular disorders
• sleep problems
• loss of memory
• mental impairment
• asterixis
• peripheral neuropathy
accumulation of nitrogenous waste products from protein metabolism
⇧ infections due to leukocyte suppression by uremic toxins
pericarditis from irritation by uremic toxins
loss of renal functions including
failure to excrete
hyperkalemia (see map)
⇩ K+ secretion
metabolic acidosis non-anion gap (see map)
prevents acids from being excreted in form of ammonium
⇩ ammonia production
can lead to anion gap metabolic acidosis (see map)
organic acids accumulate
uric acid retention
Na+ and water retention
volume and salt overload can lead to: congestive heart failure (see map) hypertension (see map)
accelerated atherosclerosis (see map)
failure to synthesize / absorb / secrete appropriate amounts of renal products
⇩ 1,25 Vit D hydroxylation
PO4- retention
⇩ Ca+ resorption
2° hyperparathyroidism
• renal osteodystrophy
• osteomalacia (see map)
• osteoporosis (see map)
decreased synthesis of erythropoietin leads to normocytic normochromic anemia (see anemia of chronic disease map)
fatigue
abnormal hemostasis leads to:
• bruising
• spontaneous GI bleed
• spontaneous cerebrovascular hemorrhage
• prolonged bleeding time
• decreased platelet factor III
• abnormal platelet aggregation and adhesiveness



3 major etiologies of glomerulonephritis

post infectious:
- streptococcal (most common)
- hepatitis B and C (see maps)
- HIV (see map)
- malaria
- toxoplasmosis

primary renal disease:
- membranoproliferative GN
- mesangial GN
- idiopathic RPGN
- Berger
- Alport
- IgA

systemic disease:
- Wegener's granulomatosis
- hypersensitivity vasculitis
- cryoglobulinemia
- systemic lupus erythematosis (see map)
- polyarteritis nodosa
- Henoch-Schonlein purpura
- Goodpasture's syndrome

primary glomerulonephritides

secondary glomerular disease

initiates immune reaction

humoral reaction can occur 1 of 3 ways

- antibodies attack fixed or planted antigen in situ within glomerulus
- circulating antibody-antigen immune complex deposits within glomerulus
- cytotoxic antibody attacks glomerular cell components

cell-mediated reaction

sensitized T cells attack glomerulus

acute inflammation (see map)

can lead to 1 of 5 clinical syndromes:

hallmark sign in urinalysis of glomerulonephritis is dysmorphic **RBC and RBC casts**

asymptomatic hematuria

gross or microscopic hematuria

eg. IgA nephropathy

acute glomerulonephritis

acute nephritic syndrome:
- abrupt onset macroscopic hematuria
- oliguria
- acute renal failure
- edema
- hypertension
- variable proteinuria

eg. poststreptococcal GN

rapidly progressing glomerulonephritis (aka crescentic GN)

- **acute nephritis**
- proteinuria
- azotemia
- rapidly ⇩ renal function
- focal segmental necrosis

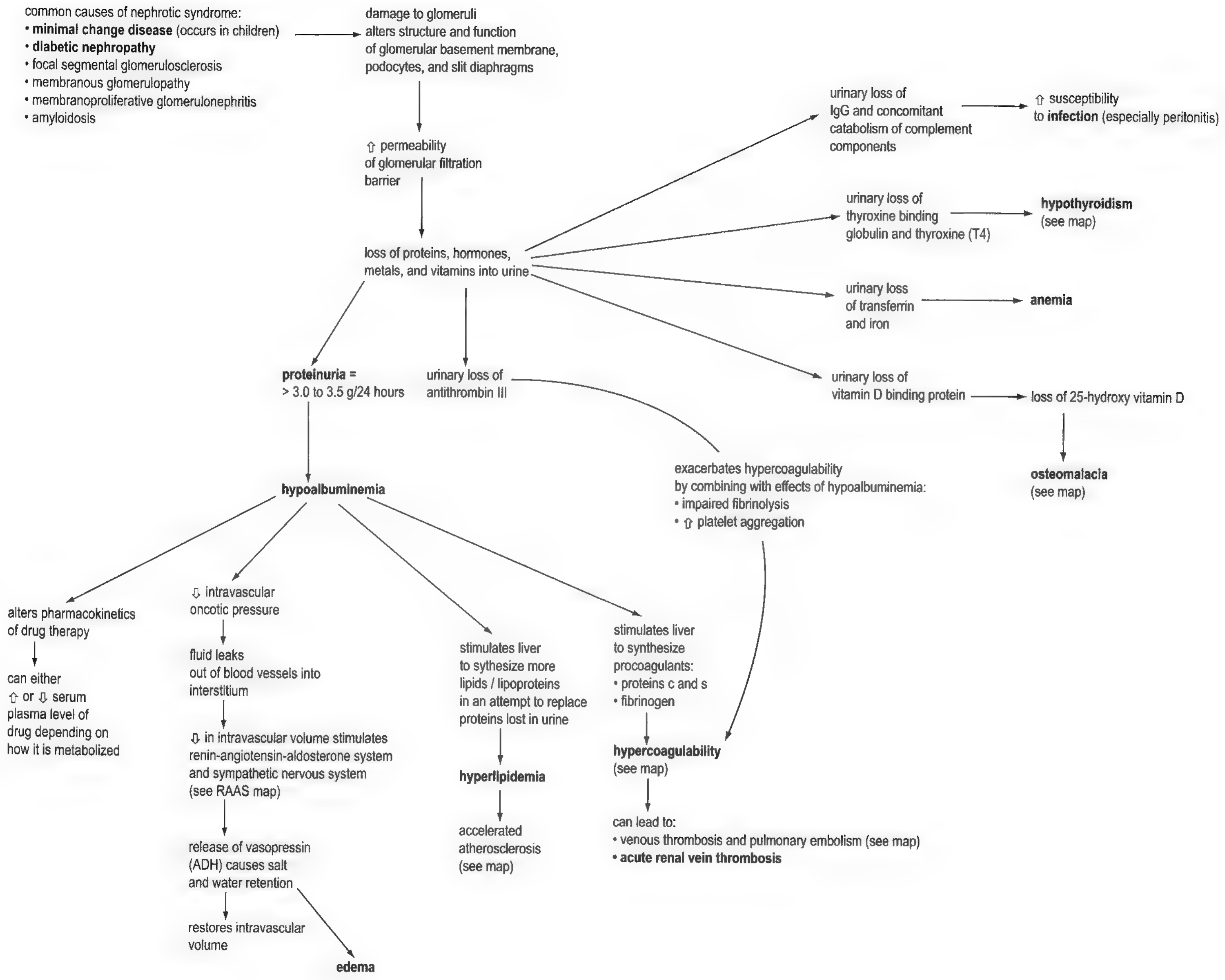
can lead to **end-stage renal failure** within days to weeks

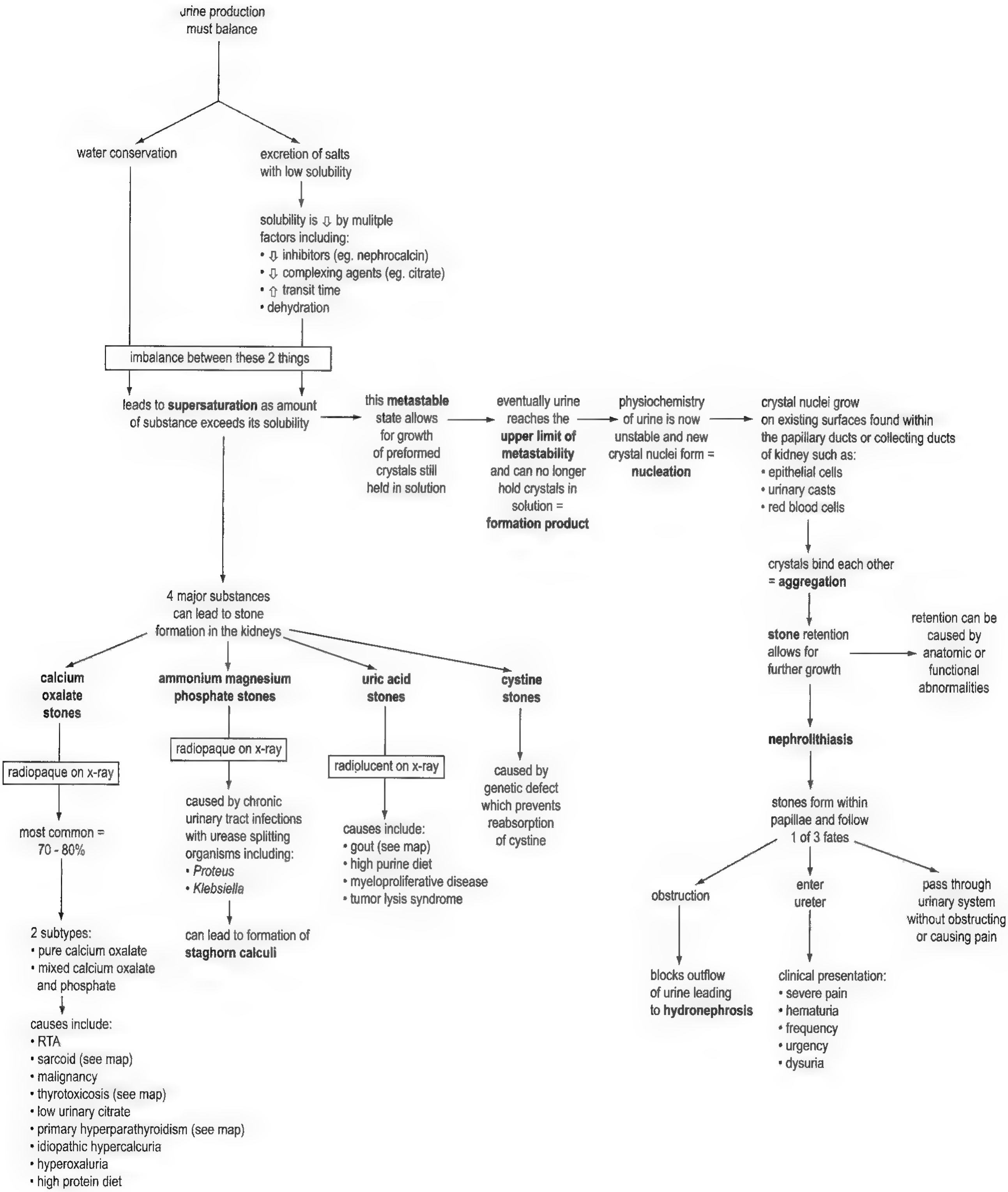
3 categories determined by early renal biopsy:
- Type 1 (anti-GBM disease) = Goodpasture's syndrome
- Type 2 (immune) = postinfectious, SLE (see map)
- Type 3 (pauci-immune) = Wegener's granulomatosis

nephrotic syndrome (see map)

chronic glomerulonephritis

progressive renal insufficiency which can lead to **end-stage renal failure** (see chronic renal failure map)


common causes of nephrotic syndrome:
• **minimal change disease** (occurs in children)
• **diabetic nephropathy**
• focal segmental glomerulosclerosis
• membranous glomerulopathy
• membranoproliferative glomerulonephritis
• amyloidosis
damage to glomeruli alters structure and function of glomerular basement membrane, podocytes, and slit diaphragms
⇧ permeability of glomerular **filtration** barrier
loss of proteins, hormones, metals, and vitamins into urine
urinary loss of IgG and concomitant catabolism of complement components
⇧ susceptibility to **infection** (especially peritonitis)
urinary loss of thyroxine binding globulin and thyroxine (T4)
hypothyroidism (see map)
urinary loss of transferrin and iron
anemia
urinary loss of vitamin D binding protein
loss of 25-hydroxy vitamin D
osteomalacia (see map)
proteinuria = > 3.0 to 3.5 g/24 hours
urinary loss of antithrombin III
exacerbates hypercoagulability by combining with effects of hypoalbuminemia:
• impaired fibrinolysis
• ⇧ platelet aggregation
hypoalbuminemia
alters pharmacokinetics of drug therapy
can either ⇧ or ⇩ serum plasma level of drug depending on how it is metabolized
⇩ intravascular oncotic pressure
fluid leaks out of blood vessels into interstitium
⇩ in intravascular volume stimulates renin-angiotensin-aldosterone system and sympathetic nervous system (see RAAS map)
release of vasopressin (ADH) causes salt and water retention
restores intravascular volume
edema
stimulates liver to sythesize more lipids / lipoproteins in an attempt to replace proteins lost in urine
hyperlipidemia
accelerated atherosclerosis (see map)
stimulates liver to synthesize procoagulants:
• proteins c and s
• fibrinogen
hypercoagulability (see map)
can lead to:
• venous thrombosis and pulmonary embolism (see map)
• **acute renal vein thrombosis**



urine production must balance

water conservation

excretion of salts with low solubility

solubility is ⇩ by mulitple factors including:
- ⇩ inhibitors (eg. nephrocalcin)
- ⇩ complexing agents (eg. citrate)
- ⇧ transit time
- dehydration

imbalance between these 2 things

leads to **supersaturation** as amount of substance exceeds its solubility

this **metastable** state allows for growth of preformed crystals still held in solution

eventually urine reaches the **upper limit of metastability** and can no longer hold crystals in solution = **formation product**

physiochemistry of urine is now unstable and new crystal nuclei form = **nucleation**

crystal nuclei grow on existing surfaces found within the papillary ducts or collecting ducts of kidney such as:
- epithelial cells
- urinary casts
- red blood cells

crystals bind each other = **aggregation**

stone retention allows for further growth

retention can be caused by anatomic or functional abnormalities

nephrolithiasis

stones form within papillae and follow 1 of 3 fates

obstruction

blocks outflow of urine leading to **hydronephrosis**

enter ureter

clinical presentation:
- severe pain
- hematuria
- frequency
- urgency
- dysuria

pass through urinary system without obstructing or causing pain

4 major substances can lead to stone formation in the kidneys

calcium oxalate stones

radiopaque on x-ray

most common = 70 - 80%

2 subtypes:
- pure calcium oxalate
- mixed calcium oxalate and phosphate

causes include:
- RTA
- sarcoid (see map)
- malignancy
- thyrotoxicosis (see map)
- low urinary citrate
- primary hyperparathyroidism (see map)
- idiopathic hypercalcuria
- hyperoxaluria
- high protein diet

ammonium magnesium phosphate stones

radiopaque on x-ray

caused by chronic urinary tract infections with urease splitting organisms including:
- *Proteus*
- *Klebsiella*

can lead to formation of **staghorn calculi**

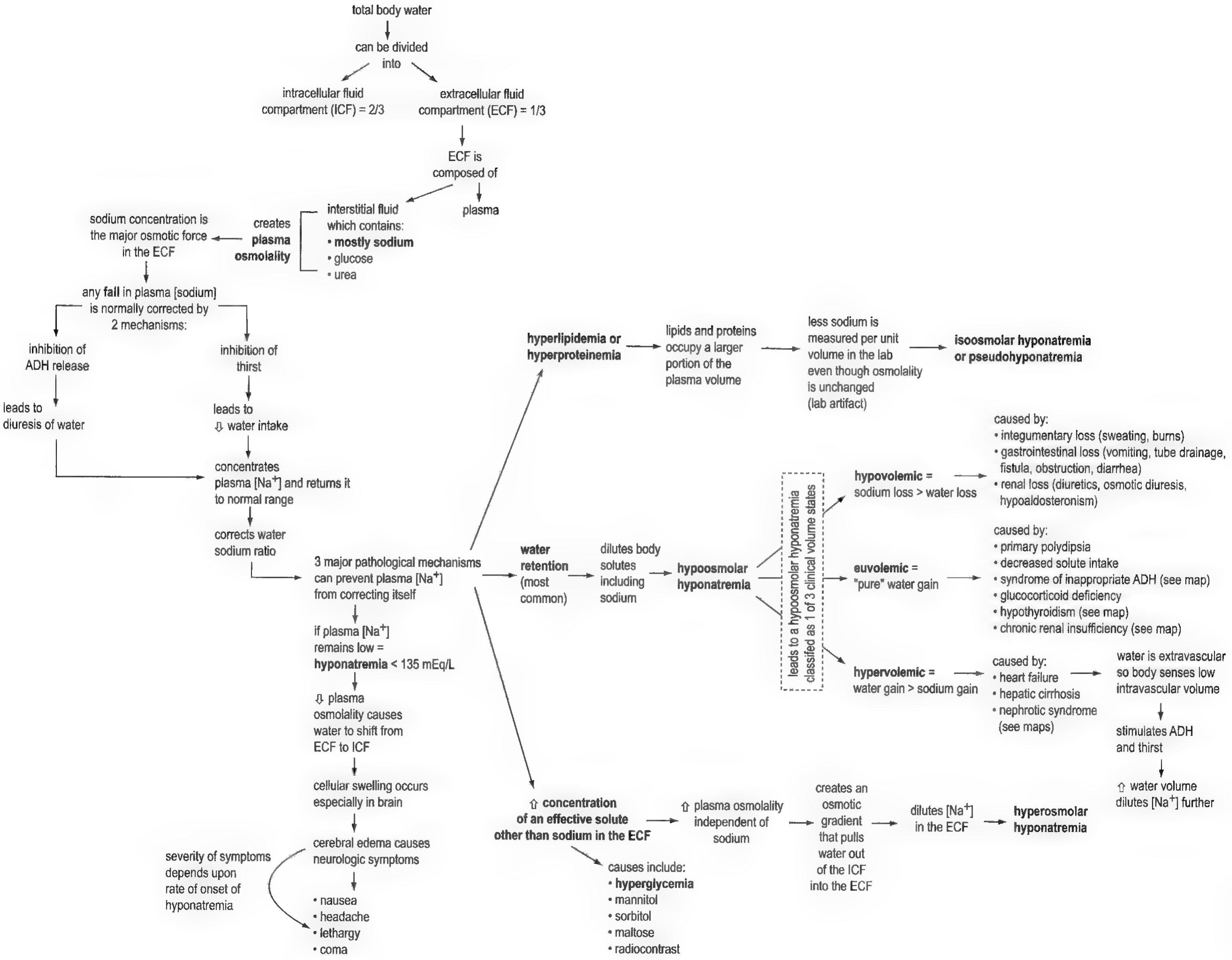
uric acid stones

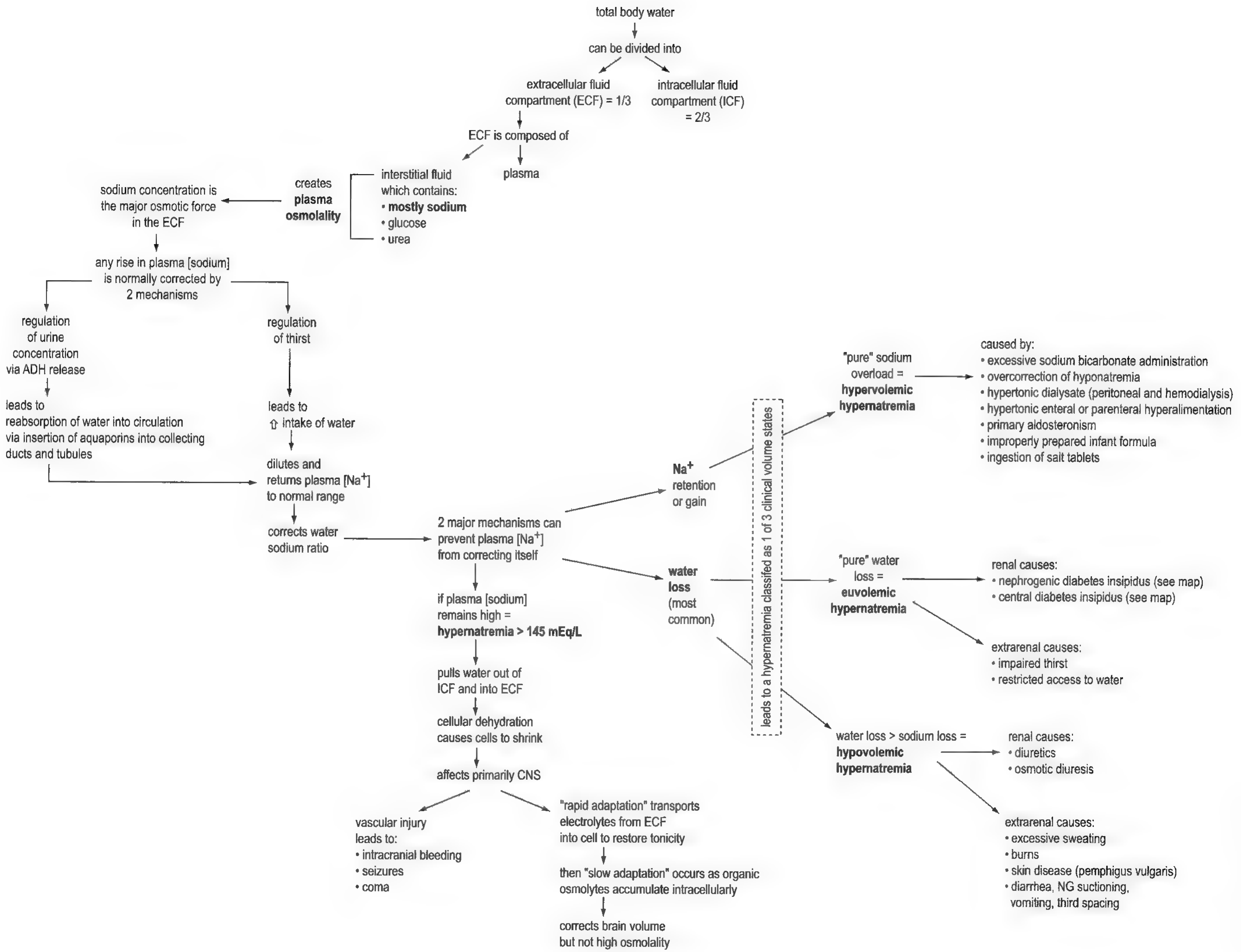
radiolucent on x-ray

causes include:
- gout (see map)
- high purine diet
- myeloproliferative disease
- tumor lysis syndrome

cystine stones

caused by genetic defect which prevents reabsorption of cystine


total body water
can be divided into
intracellular fluid compartment (ICF) = 2/3
extracellular fluid compartment (ECF) = 1/3
ECF is composed of
interstitial fluid which contains:
• **mostly sodium**
• glucose
• urea
plasma
creates **plasma osmolality**
sodium concentration is the major osmotic force in the ECF
any **fall** in plasma [sodium] is normally corrected by 2 mechanisms:
inhibition of ADH release
leads to diuresis of water
inhibition of thirst
leads to ⇩ water intake
concentrates plasma $[Na^+]$ and returns it to normal range
corrects water sodium ratio
3 major pathological mechanisms can prevent plasma $[Na^+]$ from correcting itself
if plasma $[Na^+]$ remains low = **hyponatremia** < 135 mEq/L
⇩ plasma osmolality causes water to shift from ECF to ICF
cellular swelling occurs especially in brain
cerebral edema causes neurologic symptoms
• nausea
• headache
• lethargy
• coma
severity of symptoms depends upon rate of onset of hyponatremia
hyperlipidemia or hyperproteinemia
lipids and proteins occupy a larger portion of the plasma volume
less sodium is measured per unit volume in the lab even though osmolality is unchanged (lab artifact)
isoosmolar hyponatremia or pseudohyponatremia
water retention (most common)
dilutes body solutes including sodium
hypoosmolar hyponatremia
leads to a hypoosmolar hyponatremia classifed as 1 of 3 clinical volume states
hypovolemic = sodium loss > water loss
caused by:
• integumentary loss (sweating, burns)
• gastrointestinal loss (vomiting, tube drainage, fistula, obstruction, diarrhea)
• renal loss (diuretics, osmotic diuresis, hypoaldosteronism)
euvolemic = "pure" water gain
caused by:
• primary polydipsia
• decreased solute intake
• syndrome of inappropriate ADH (see map)
• glucocorticoid deficiency
• hypothyroidism (see map)
• chronic renal insufficiency (see map)
hypervolemic = water gain > sodium gain
caused by:
• heart failure
• hepatic cirrhosis
• nephrotic syndrome (see maps)
water is extravascular so body senses low intravascular volume
stimulates ADH and thirst
⇧ water volume dilutes $[Na^+]$ further
⇧ concentration of an effective solute other than sodium in the ECF
causes include:
• **hyperglycemia**
• mannitol
• sorbitol
• maltose
• radiocontrast
⇧ plasma osmolality independent of sodium
creates an osmotic gradient that pulls water out of the ICF into the ECF
dilutes $[Na^+]$ in the ECF
hyperosmolar hyponatremia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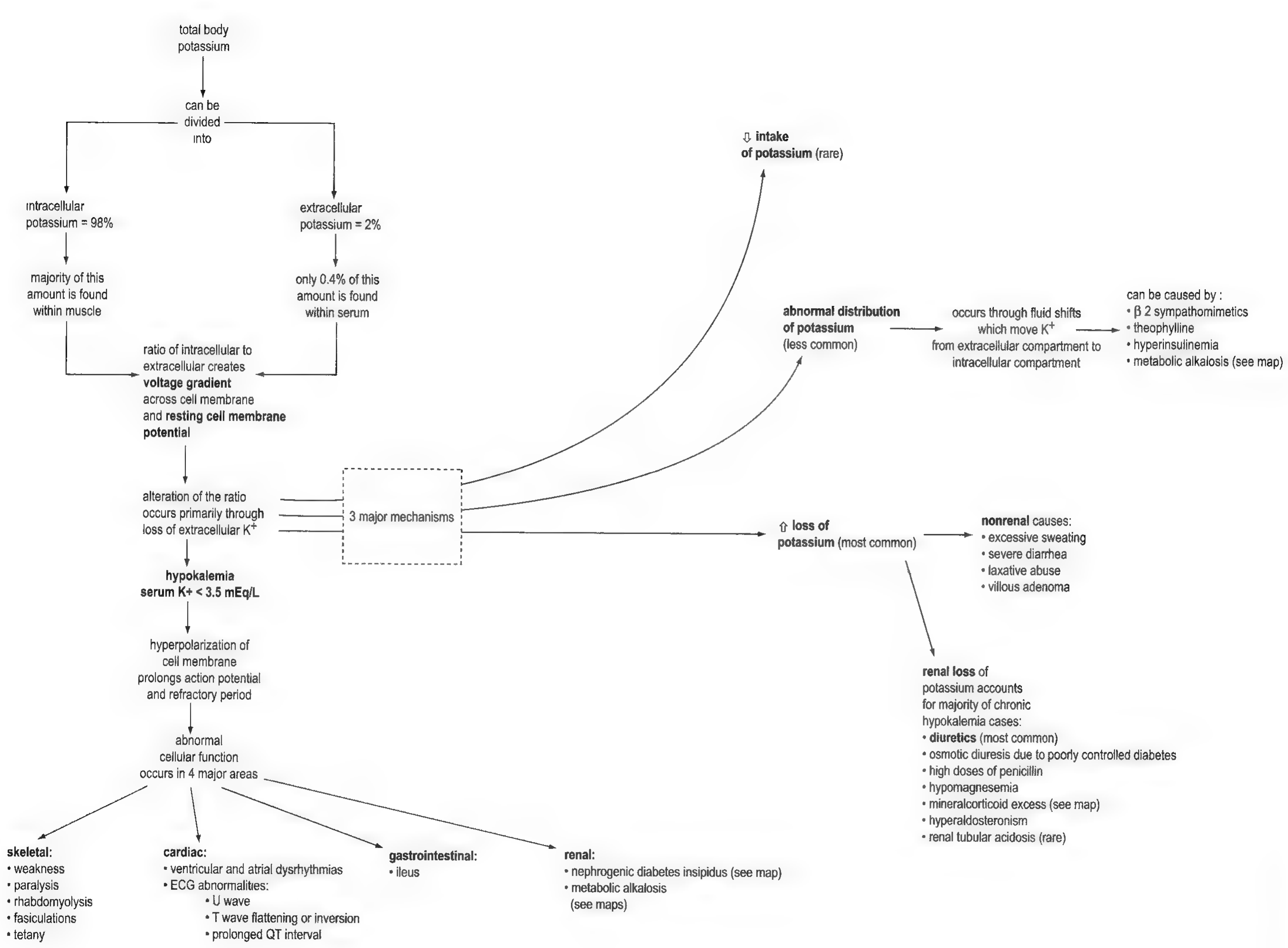
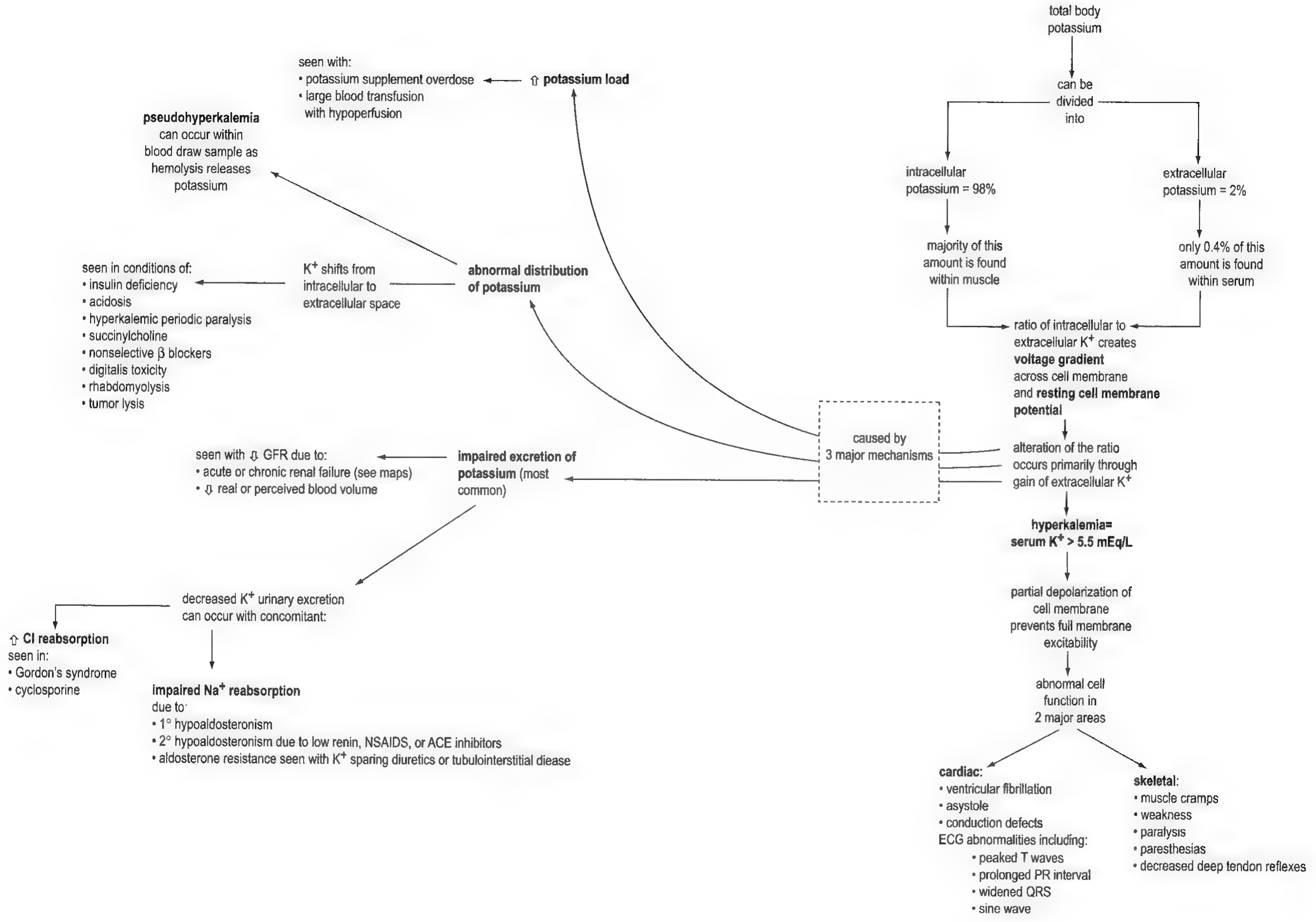
ECF is composed of
plasma
interstitial fluid which contains:
• **mostly sodium**
• glucose
• urea
creates **plasma osmolality**
sodium concentration is the major osmotic force in the ECF
any rise in plasma [sodium] is normally corrected by 2 mechanisms
regulation of urine concentration via ADH release
leads to reabsorption of water into circulation via insertion of aquaporins into collecting ducts and tubules
regulation of thirst
leads to ⇧ intake of water
dilutes and returns plasma [Na$^+$] to normal range
corrects water sodium ratio
2 major mechanisms can prevent plasma [Na$^+$] from correcting itself
Na$^+$ retention or gain
water loss (most common)
leads to a hypernatremia classifed as 1 of 3 clinical volume states
"pure" sodium overload = **hypervolemic hypernatremia**
caused by:
• excessive sodium bicarbonate administration
• overcorrection of hyponatremia
• hypertonic dialysate (peritoneal and hemodialysis)
• hypertonic enteral or parenteral hyperalimentation
• primary aldosteronism
• improperly prepared infant formula
• ingestion of salt tablets
"pure" water loss = **euvolemic hypernatremia**
renal causes:
• nephrogenic diabetes insipidus (see map)
• central diabetes insipidus (see map)
extrarenal causes:
• impaired thirst
• restricted access to water
water loss > sodium loss = **hypovolemic hypernatremia**
renal causes:
• diuretics
• osmotic diuresis
extrarenal causes:
• excessive sweating
• burns
• skin disease (pemphigus vulgaris)
• diarrhea, NG suctioning, vomiting, third spacing
if plasma [sodium] remains high = **hypernatremia > 145 mEq/L**
pulls water out of ICF and into ECF
cellular dehydration causes cells to shrink
affects primarily CNS
vascular injury leads to:
• intracranial bleeding
• seizures
• coma
"rapid adaptation" transports electrolytes from ECF into cell to restore tonicity
then "slow adaptation" occurs as organic osmolytes accumulate intracellularly
corrects brain volume but not high osmolality


total body potassium
can be divided into
intracellular potassium = 98%
extracellular potassium = 2%
majority of this amount is found within muscle
only 0.4% of this amount is found within serum
ratio of intracellular to extracellular creates **voltage gradient** across cell membrane and **resting cell membrane potential**
alteration of the ratio occurs primarily through loss of extracellular K^+
3 major mechanisms
⇩ **intake of potassium** (rare)
abnormal distribution of potassium (less common)
occurs through fluid shifts which move K^+ from extracellular compartment to intracellular compartment
can be caused by :
• β 2 sympathomimetics
• theophylline
• hyperinsulinemia
• metabolic alkalosis (see map)
⇧ **loss of potassium** (most common)
nonrenal causes:
• excessive sweating
• severe diarrhea
• laxative abuse
• villous adenoma
renal loss of potassium accounts for majority of chronic hypokalemia cases:
• **diuretics** (most common)
• osmotic diuresis due to poorly controlled diabetes
• high doses of penicillin
• hypomagnesemia
• mineralcorticoid excess (see map)
• hyperaldosteronism
• renal tubular acidosis (rare)
hypokalemia serum K+ < 3.5 mEq/L
hyperpolarization of cell membrane prolongs action potential and refractory period
abnormal cellular function occurs in 4 major areas
skeletal:
• weakness
• paralysis
• rhabdomyolysis
• fasiculations
• tetany
cardiac:
• ventricular and atrial dysrhythmias
• ECG abnormalities:
• U wave
• T wave flattening or inversion
• prolonged QT interval
gastrointestinal:
• ileus
renal:
• nephrogenic diabetes insipidus (see map)
• metabolic alkalosis (see maps)



total body potassium

can be divided into

intracellular potassium = 98%

majority of this amount is found within muscle

extracellular potassium = 2%

only 0.4% of this amount is found within serum

ratio of intracellular to extracellular K+ creates **voltage gradient** across cell membrane and **resting cell membrane potential**

alteration of the ratio occurs primarily through gain of extracellular K+

hyperkalemia= serum K+ > 5.5 mEq/L

partial depolarization of cell membrane prevents full membrane excitability

abnormal cell function in 2 major areas

cardiac:
- ventricular fibrillation
- asystole
- conduction defects

ECG abnormalities including:
  - peaked T waves
  - prolonged PR interval
  - widened QRS
  - sine wave

skeletal:
- muscle cramps
- weakness
- paralysis
- paresthesias
- decreased deep tendon reflexes

caused by 3 major mechanisms

⇧ **potassium load**

seen with:
- potassium supplement overdose
- large blood transfusion with hypoperfusion

abnormal distribution of potassium

pseudohyperkalemia can occur within blood draw sample as hemolysis releases potassium

K+ shifts from intracellular to extracellular space

seen in conditions of:
- insulin deficiency
- acidosis
- hyperkalemic periodic paralysis
- succinylcholine
- nonselective β blockers
- digitalis toxicity
- rhabdomyolysis
- tumor lysis

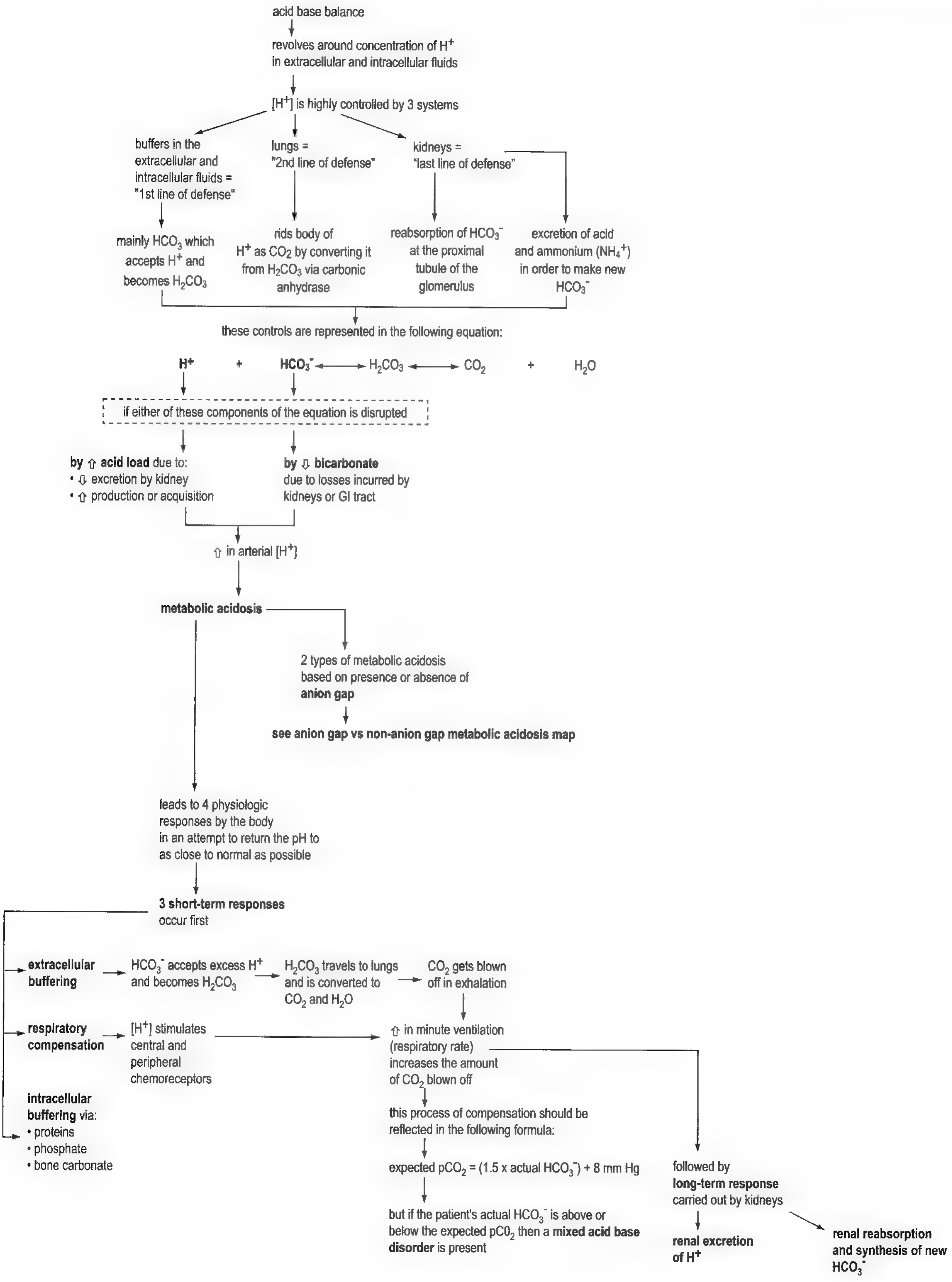
impaired excretion of potassium (most common)

seen with ⇩ GFR due to:
- acute or chronic renal failure (see maps)
- ⇩ real or perceived blood volume

decreased K+ urinary excretion can occur with concomitant:

⇧ **Cl reabsorption**
seen in:
- Gordon's syndrome
- cyclosporine

impaired Na+ reabsorption
due to:
- 1° hypoaldosteronism
- 2° hypoaldosteronism due to low renin, NSAIDS, or ACE inhibitors
- aldosterone resistance seen with K+ sparing diuretics or tubulointerstitial diease



acid base balance

revolves around concentration of H^+ in extracellular and intracellular fluids

$[H^+]$ is highly controlled by 3 systems

buffers in the extracellular and intracellular fluids = "1st line of defense"

mainly HCO_3 which accepts H^+ and becomes H_2CO_3

lungs = "2nd line of defense"

rids body of H^+ as CO_2 by converting it from H_2CO_3 via carbonic anhydrase

kidneys = "last line of defense"

reabsorption of HCO_3^- at the proximal tubule of the glomerulus

excretion of acid and ammonium (NH_4^+) in order to make new HCO_3^-

these controls are represented in the following equation:

$$\mathbf{H^+} + \mathbf{HCO_3^-} \longleftrightarrow H_2CO_3 \longleftrightarrow CO_2 + H_2O$$

if either of these components of the equation is disrupted

by ⇧ acid load due to:
- ⇩ excretion by kidney
- ⇧ production or acquisition

by ⇩ bicarbonate due to losses incurred by kidneys or GI tract

⇧ in arterial $[H^+]$

metabolic acidosis

2 types of metabolic acidosis based on presence or absence of **anion gap**

see anion gap vs non-anion gap metabolic acidosis map

leads to 4 physiologic responses by the body in an attempt to return the pH to as close to normal as possible

3 short-term responses occur first

extracellular buffering → HCO_3^- accepts excess H^+ and becomes H_2CO_3 → H_2CO_3 travels to lungs and is converted to CO_2 and H_2O → CO_2 gets blown off in exhalation

respiratory compensation → $[H^+]$ stimulates central and peripheral chemoreceptors

⇧ in minute ventilation (respiratory rate) increases the amount of CO_2 blown off

this process of compensation should be reflected in the following formula:

expected $pCO_2 = (1.5 \times \text{actual } HCO_3^-) + 8$ mm Hg

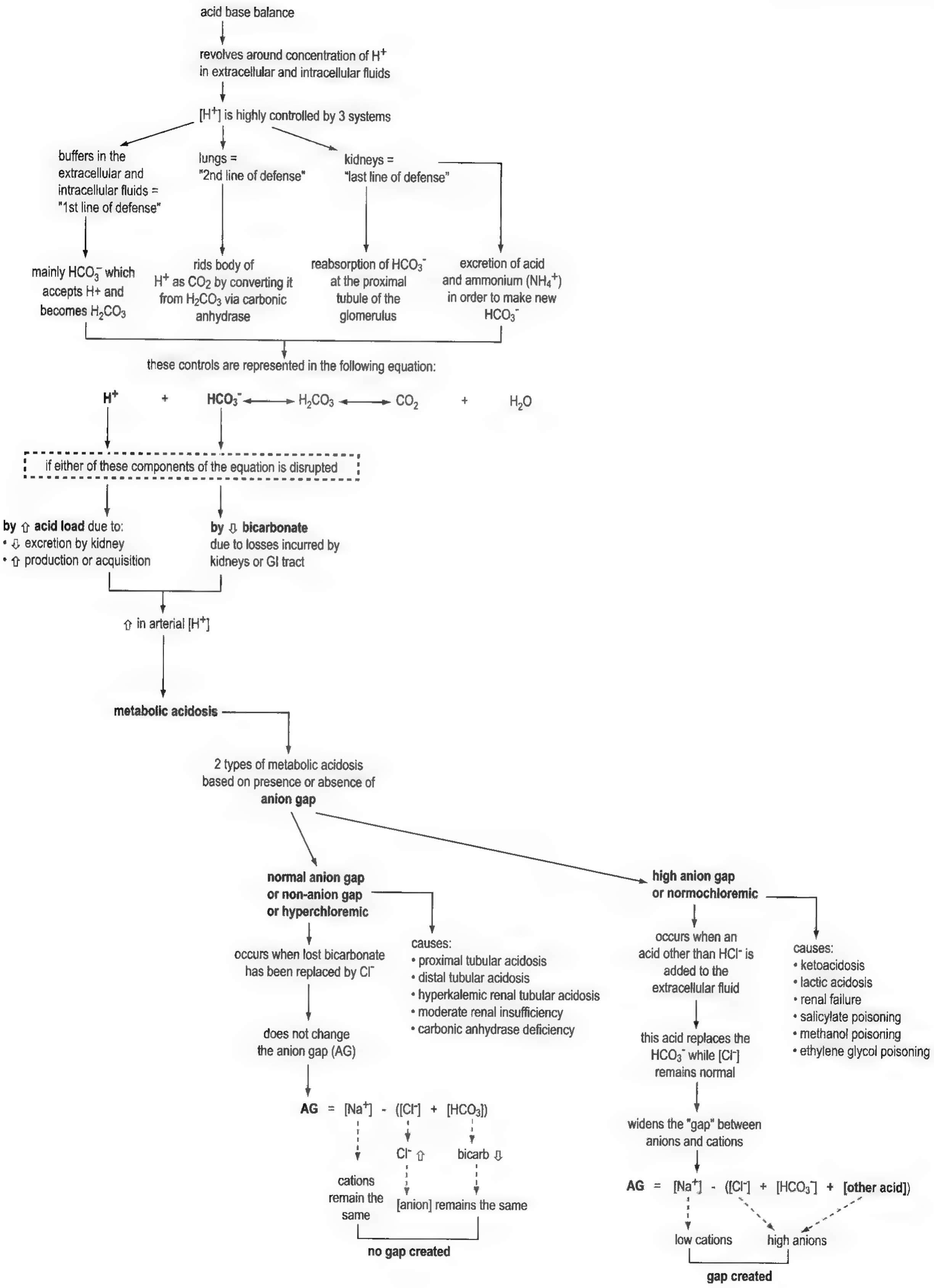
but if the patient's actual HCO_3^- is above or below the expected $pC0_2$ then a **mixed acid base disorder** is present

intracellular buffering via:
- proteins
- phosphate
- bone carbonate

followed by **long-term response** carried out by kidneys

renal excretion of H^+

renal reabsorption and synthesis of new HCO_3^-



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⇧ in arterial $[H^+]$

metabolic acidosis

2 types of metabolic acidosis based on presence or absence of **anion gap**

normal anion gap or non-anion gap or hyperchloremic

occurs when lost bicarbonate has been replaced by Cl^-

does not change the anion gap (AG)

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-])$$

cations remain the same

Cl^- ⇧

bicarb ⇩

[anion] remains the same

no gap created

causes:

- proximal tubular acidosis
- distal tubular acidosis
- hyperkalemic renal tubular acidosis
- moderate renal insufficiency
- carbonic anhydrase deficiency

high anion gap or normochloremic

occurs when an acid other than HCl^- is added to the extracellular fluid

this acid replaces the HCO_3^- while $[Cl^-]$ remains normal

widens the "gap" between anions and cations

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-] + \textbf{[other acid]})$$

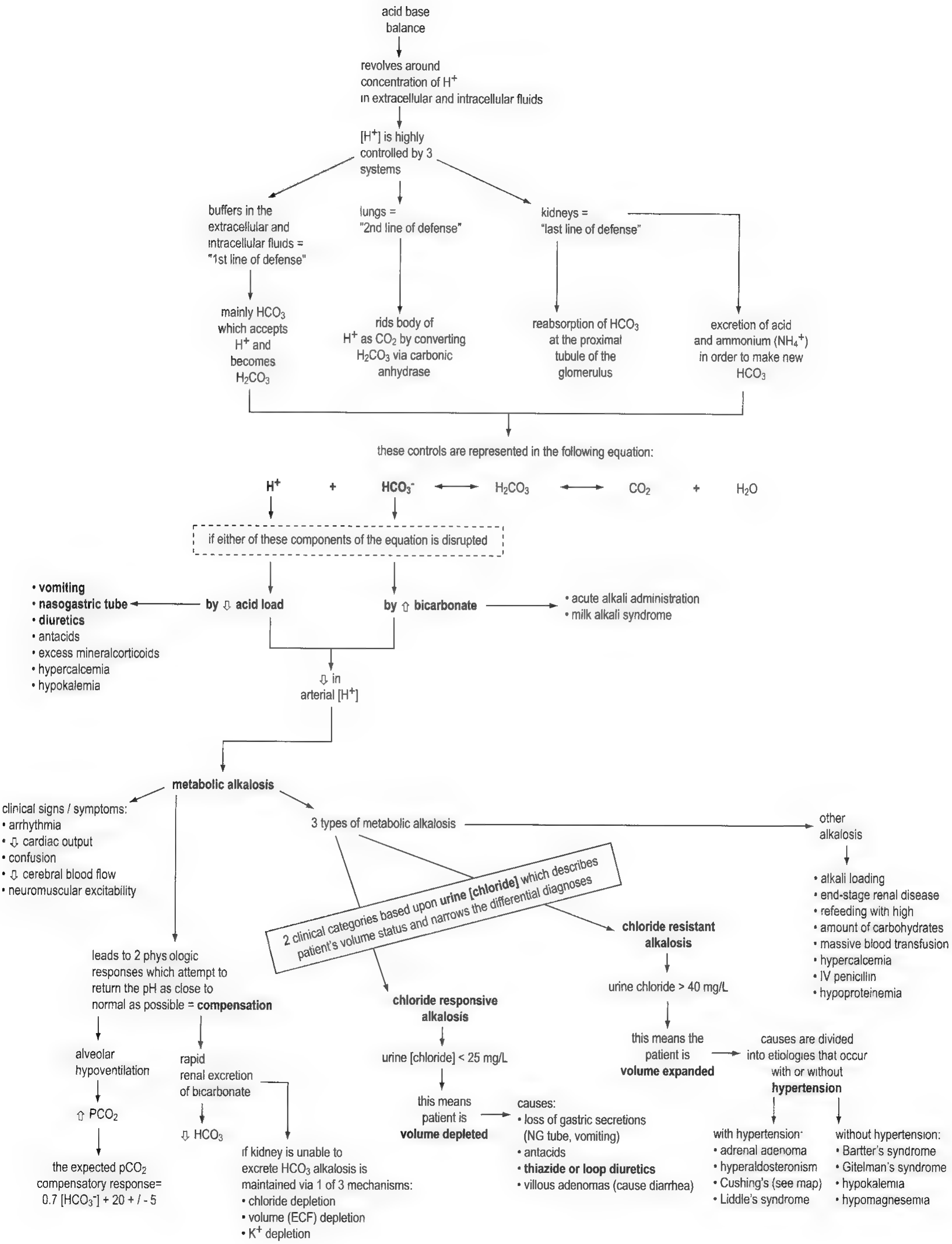
low cations

high anions

gap created

causes:

- ketoacidosis
- lactic acidosis
- renal failure
- salicylate poisoning
- methanol poisoning
- ethylene glycol poisoning



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if either of these components of the equation is disrupted

by ⇩ acid load

- **vomiting**
- **nasogastric tube**
- **diuretics**
- antacids
- excess mineralcorticoids
- hypercalcemia
- hypokalemia

by ⇧ bicarbonate

- acute alkali administration
- milk alkali syndrome

⇩ in arterial $[H^+]$

metabolic alkalosis

clinical signs / symptoms:

- arrhythmia
- ⇩ cardiac output
- confusion
- ⇩ cerebral blood flow
- neuromuscular excitability

leads to 2 physiologic responses which attempt to return the pH as close to normal as possible = **compensation**

alveolar hypoventilation

⇧ PCO_2

the expected pCO_2 compensatory response= $0.7\,[HCO_3^-] + 20 +/- 5$

rapid renal excretion of bicarbonate

⇩ HCO_3

if kidney is unable to excrete HCO_3 alkalosis is maintained via 1 of 3 mechanisms:

- chloride depletion
- volume (ECF) depletion
- K^+ depletion

3 types of metabolic alkalosis

2 clinical categories based upon **urine [chloride]** which describes patient's volume status and narrows the differential diagnoses

chloride responsive alkalosis

urine [chloride] < 25 mg/L

this means patient is **volume depleted**

causes:

- loss of gastric secretions (NG tube, vomiting)
- antacids
- **thiazide or loop diuretics**
- villous adenomas (cause diarrhea)

chloride resistant alkalosis

urine chloride > 40 mg/L

this means the patient is **volume expanded**

causes are divided into etiologies that occur with or without **hypertension**

with hypertension:

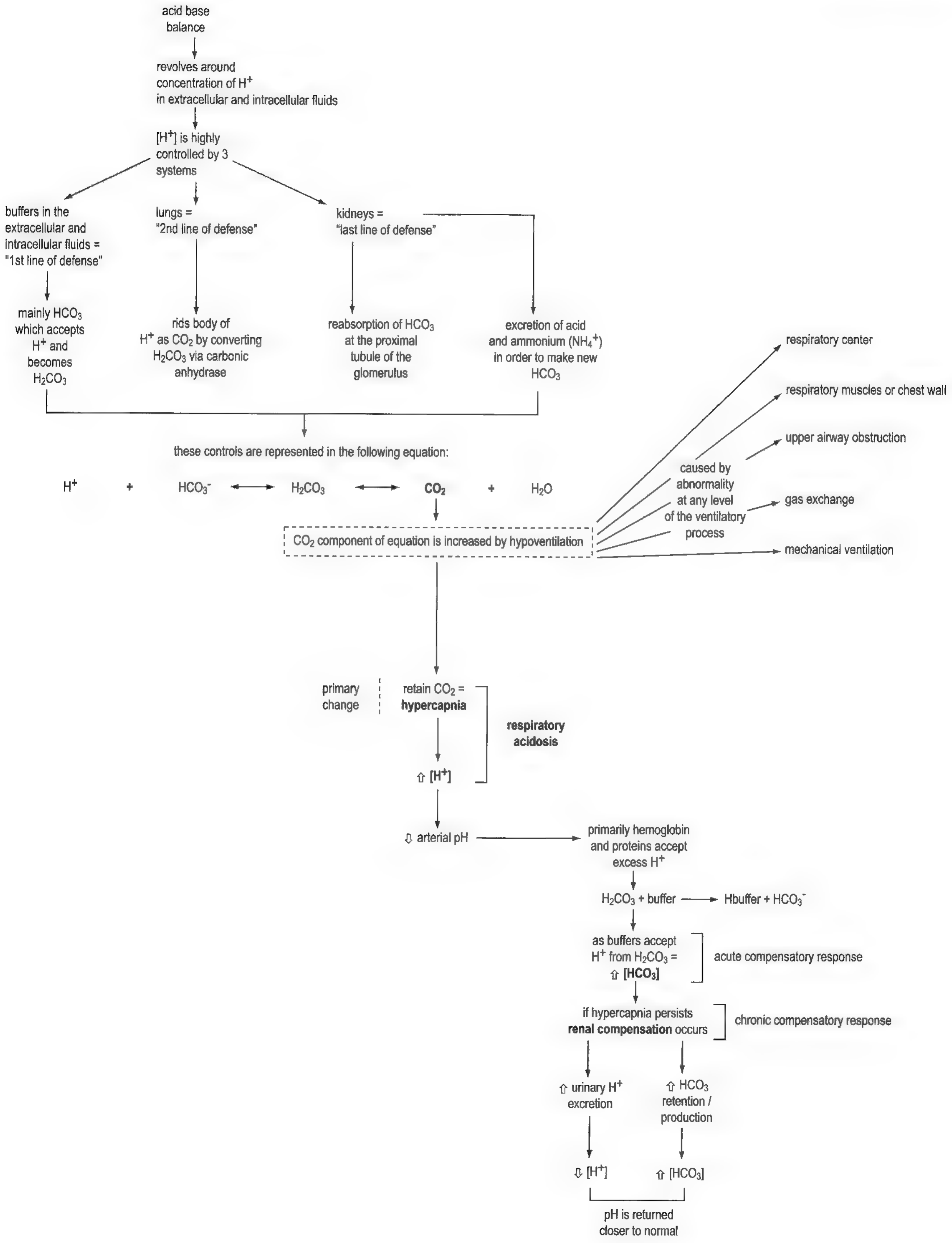
- adrenal adenoma
- hyperaldosteronism
- Cushing's (see map)
- Liddle's syndrome

without hypertension:

- Bartter's syndrome
- Gitelman's syndrome
- hypokalemia
- hypomagnesemia

other alkalosis

- alkali loading
- end-stage renal disease
- refeeding with high
- amount of carbohydrates
- massive blood transfusion
- hypercalcemia
- IV penicillin
- hypoproteinemia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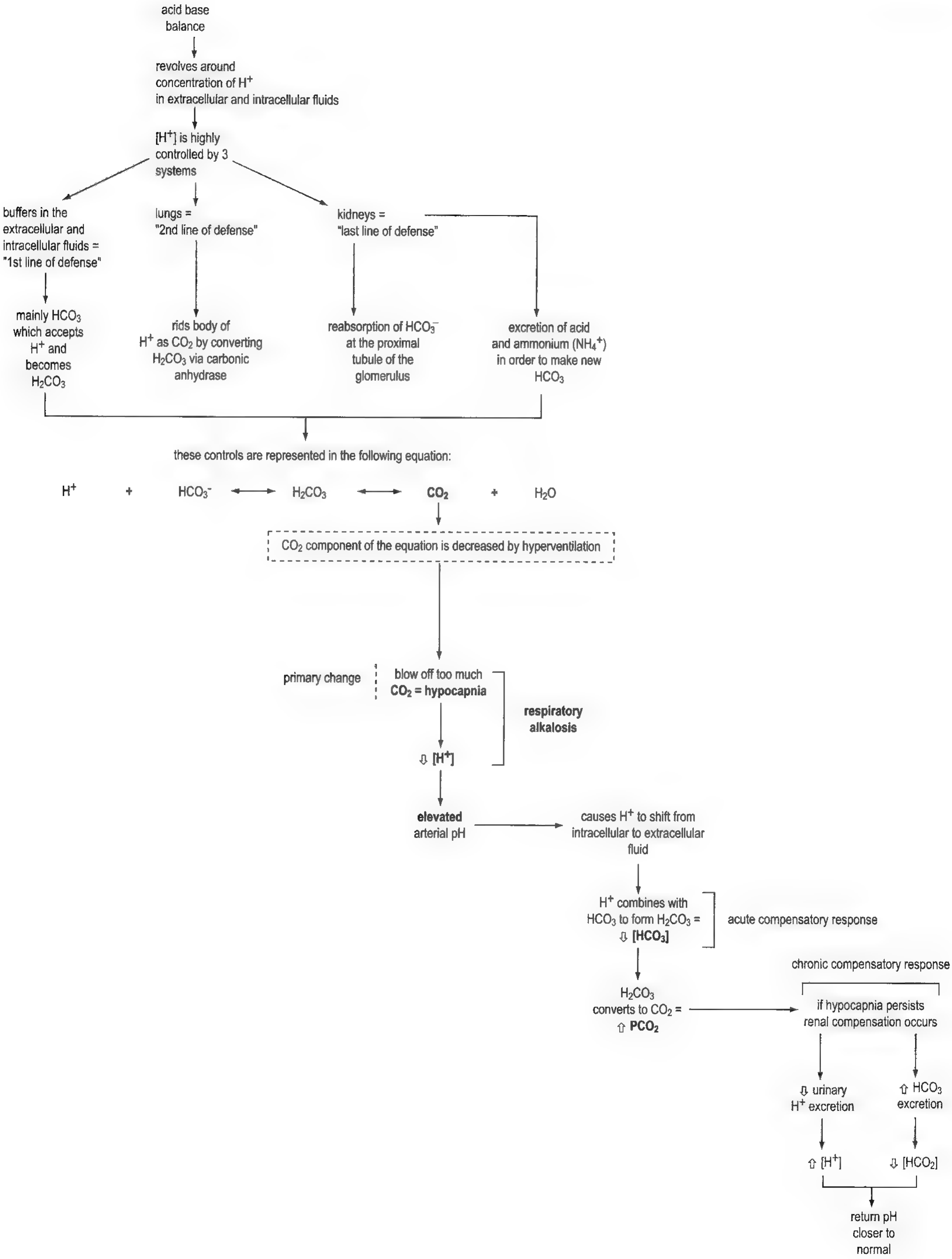
$H^+ + HCO_3^- \longleftrightarrow H_2CO_3 \longleftrightarrow CO_2 + H_2O$
CO_2 component of equation is increased by hypoventilation
caused by abnormality at any level of the ventilatory process
respiratory center
respiratory muscles or chest wall
upper airway obstruction
gas exchange
mechanical ventilation
primary change
retain CO_2 = **hypercapnia**
⇧ $[H^+]$
respiratory acidosis
⇩ arterial pH
primarily hemoglobin and proteins accept excess H^+
H_2CO_3 + buffer → Hbuffer + HCO_3^-
as buffers accept H^+ from H_2CO_3 = ⇧ $[HCO_3]$
acute compensatory response
if hypercapnia persists **renal compensation** occurs
chronic compensatory response
⇧ urinary H^+ excretion
⇧ HCO_3 retention / production
⇩ $[H^+]$
⇧ $[HCO_3]$
pH is returned closer to normal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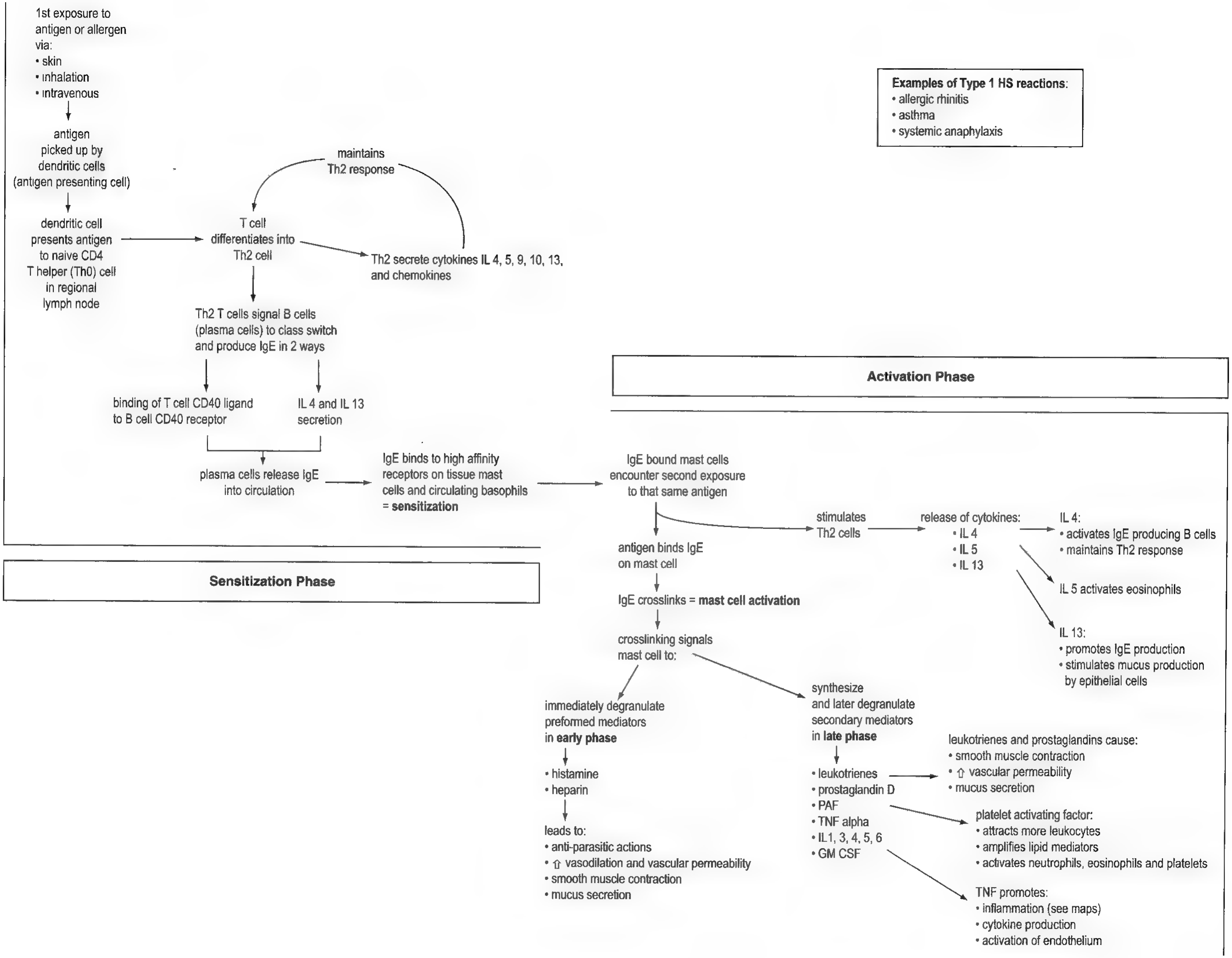
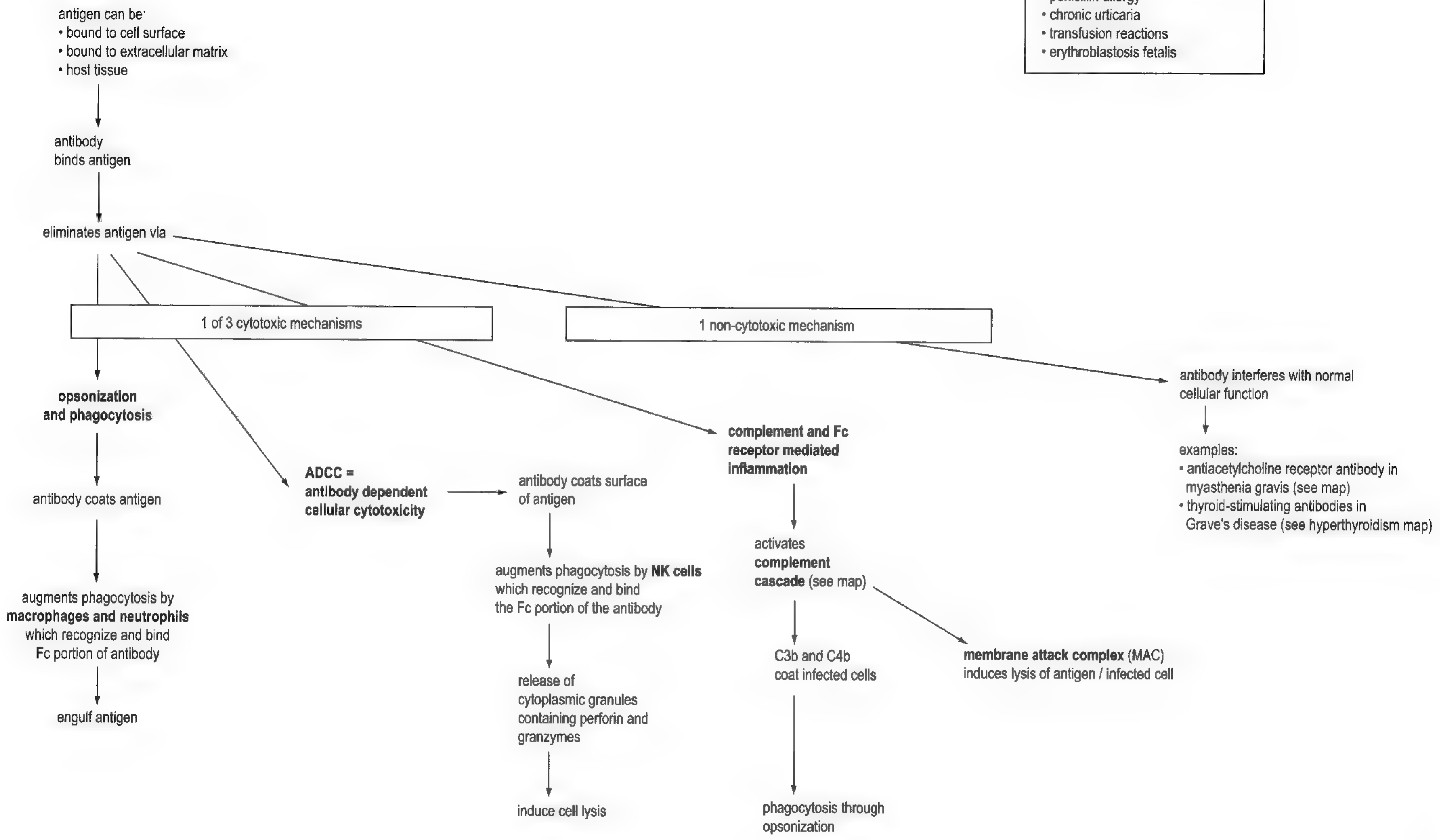
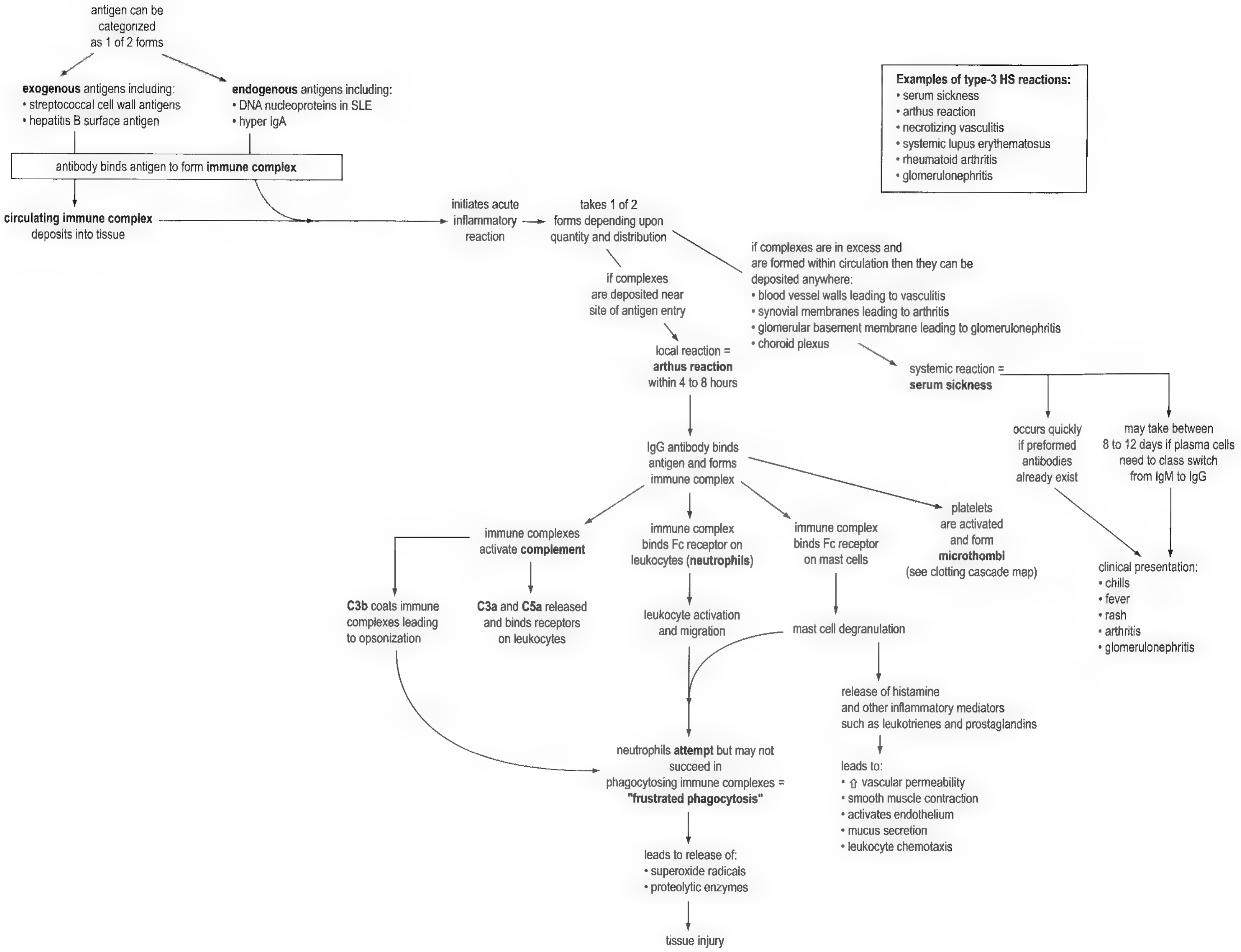
$H^+ + HCO_3^- \longleftrightarrow H_2CO_3 \longleftrightarrow CO_2 + H_2O$
CO_2 component of the equation is decreased by hyperventilation
primary change
blow off too much CO_2 = hypocapnia
⇩ $[H^+]$
respiratory alkalosis
elevated arterial pH
causes H^+ to shift from intracellular to extracellular fluid
H^+ combines with HCO_3 to form H_2CO_3 = ⇩ $[HCO_3]$
acute compensatory response
H_2CO_3 converts to CO_2 = ⇧ PCO_2
chronic compensatory response
if hypocapnia persists renal compensation occurs
⇩ urinary H^+ excretion
⇧ HCO_3 excretion
⇧ $[H^+]$
⇩ $[HCO_2]$
return pH closer to normal

Examples of Type 1 HS reactions:
- allergic rhinitis
- asthma
- systemic anaphylaxis


1st exposure to antigen or allergen via:
• skin
• inhalation
• intravenous
antigen picked up by dendritic cells (antigen presenting cell)
dendritic cell presents antigen to naive CD4 T helper (Th0) cell in regional lymph node
T cell differentiates into Th2 cell
maintains Th2 response
Th2 secrete cytokines IL 4, 5, 9, 10, 13, and chemokines
Th2 T cells signal B cells (plasma cells) to class switch and produce IgE in 2 ways
binding of T cell CD40 ligand to B cell CD40 receptor
IL 4 and IL 13 secretion
plasma cells release IgE into circulation
IgE binds to high affinity receptors on tissue mast cells and circulating basophils = sensitization
Sensitization Phase
Activation Phase
IgE bound mast cells encounter second exposure to that same antigen
stimulates Th2 cells
release of cytokines:
• IL 4
• IL 5
• IL 13
IL 4:
• activates IgE producing B cells
• maintains Th2 response
IL 5 activates eosinophils
IL 13:
• promotes IgE production
• stimulates mucus production by epithelial cells
antigen binds IgE on mast cell
IgE crosslinks = mast cell activation
crosslinking signals mast cell to:
immediately degranulate preformed mediators in early phase
• histamine
• heparin
leads to:
• anti-parasitic actions
• ⇧ vasodilation and vascular permeability
• smooth muscle contraction
• mucus secretion
synthesize and later degranulate secondary mediators in late phase
• leukotrienes
• prostaglandin D
• PAF
• TNF alpha
• IL1, 3, 4, 5, 6
• GM CSF
leukotrienes and prostaglandins cause:
• smooth muscle contraction
• ⇧ vascular permeability
• mucus secretion
platelet activating factor:
• attracts more leukocytes
• amplifies lipid mediators
• activates neutrophils, eosinophils and platelets
TNF promotes:
• inflammation (see maps)
• cytokine production
• activation of endothelium

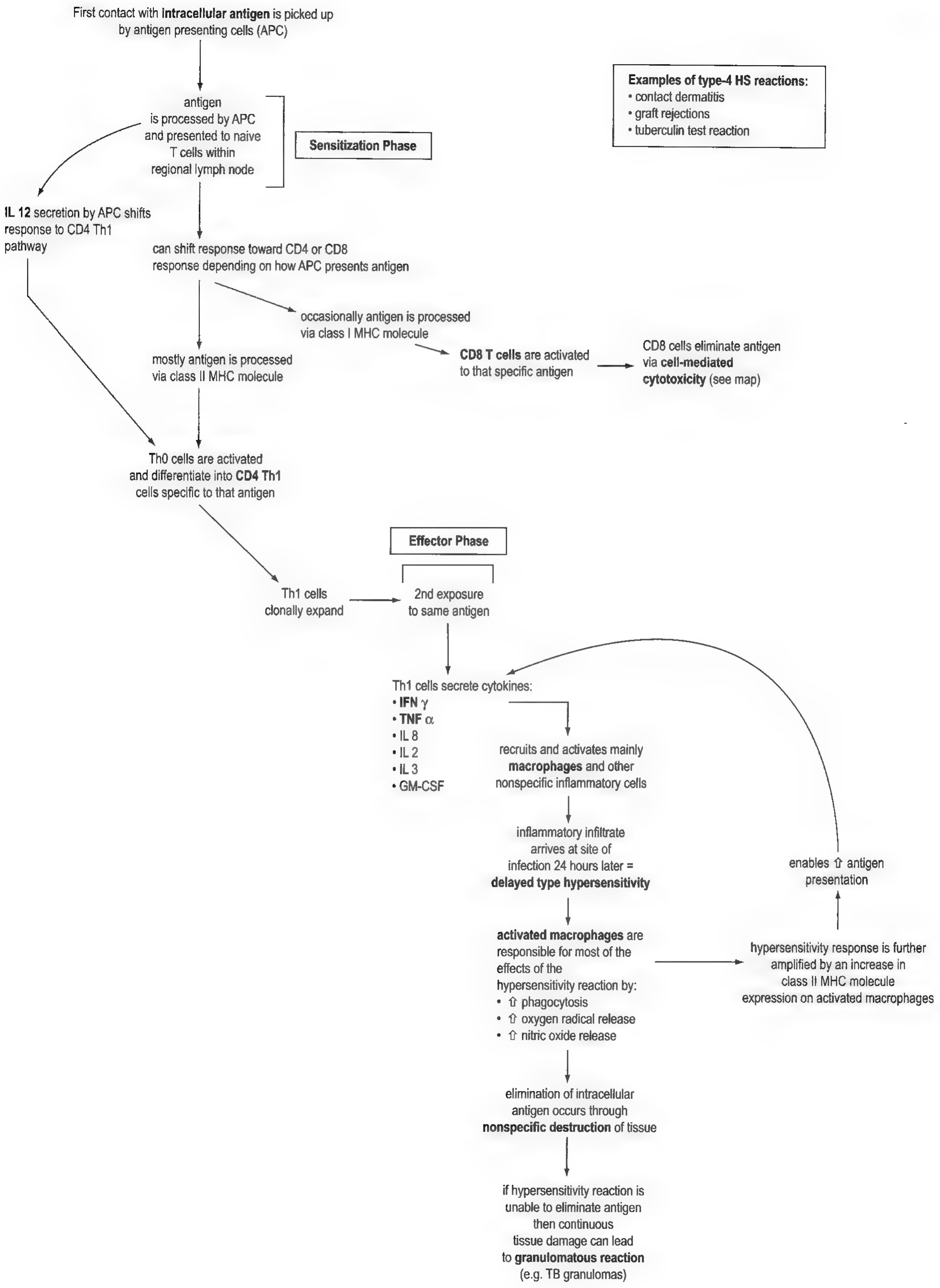
Examples of type-2 HS reactions:
- penicillin allergy
- chronic urticaria
- transfusion reactions
- erythroblastosis fetalis


antigen can be·
• bound to cell surface
• bound to extracellular matrix
• host tissue
antibody binds antigen
eliminates antigen via
1 of 3 cytotoxic mechanisms
1 non-cytotoxic mechanism
opsonization and phagocytosis
antibody coats antigen
augments phagocytosis by **macrophages and neutrophils** which recognize and bind Fc portion of antibody
engulf antigen
ADCC = antibody dependent cellular cytotoxicity
antibody coats surface of antigen
augments phagocytosis by **NK cells** which recognize and bind the Fc portion of the antibody
release of cytoplasmic granules containing perforin and granzymes
induce cell lysis
complement and Fc receptor mediated inflammation
activates **complement cascade** (see map)
C3b and C4b coat infected cells
phagocytosis through opsonization
membrane attack complex (MAC) induces lysis of antigen / infected cell
antibody interferes with normal cellular function
examples:
• antiacetylcholine receptor antibody in myasthenia gravis (see map)
• thyroid-stimulating antibodies in Grave's disease (see hyperthyroidism map)


antigen can be categorized as 1 of 2 forms
exogenous antigens including:
• streptococcal cell wall antigens
• hepatitis B surface antigen
endogenous antigens including:
• DNA nucleoproteins in SLE
• hyper IgA
antibody binds antigen to form **immune complex**
circulating immune complex deposits into tissue
initiates acute inflammatory reaction
takes 1 of 2 forms depending upon quantity and distribution
if complexes are deposited near site of antigen entry
local reaction = **arthus reaction** within 4 to 8 hours
if complexes are in excess and are formed within circulation then they can be deposited anywhere:
• blood vessel walls leading to vasculitis
• synovial membranes leading to arthritis
• glomerular basement membrane leading to glomerulonephritis
• choroid plexus
systemic reaction = **serum sickness**
occurs quickly if preformed antibodies already exist
may take between 8 to 12 days if plasma cells need to class switch from IgM to IgG
clinical presentation:
• chills
• fever
• rash
• arthritis
• glomerulonephritis
IgG antibody binds antigen and forms immune complex
immune complexes activate **complement**
immune complex binds Fc receptor on leukocytes (**neutrophils**)
immune complex binds Fc receptor on mast cells
platelets are activated and form **microthombi** (see clotting cascade map)
C3b coats immune complexes leading to opsonization
C3a and **C5a** released and binds receptors on leukocytes
leukocyte activation and migration
mast cell degranulation
release of histamine and other inflammatory mediators such as leukotrienes and prostaglandins
leads to:
• ⇧ vascular permeability
• smooth muscle contraction
• activates endothelium
• mucus secretion
• leukocyte chemotaxis
neutrophils **attempt** but may not succeed in phagocytosing immune complexes = **"frustrated phagocytosis"**
leads to release of:
• superoxide radicals
• proteolytic enzymes
tissue injury

Examples of type-3 HS reactions:
- serum sickness
- arthus reaction
- necrotizing vasculitis
- systemic lupus erythematosus
- rheumatoid arthritis
- glomerulonephritis

Examples of type-4 HS reactions:
- contact dermatitis
- graft rejections
- tuberculin test reaction



First contact with **intracellular antigen** is picked up by antigen presenting cells (APC)

antigen is processed by APC and presented to naive T cells within regional lymph node

Sensitization Phase

IL 12 secretion by APC shifts response to CD4 Th1 pathway

can shift response toward CD4 or CD8 response depending on how APC presents antigen

occasionally antigen is processed via class I MHC molecule

CD8 T cells are activated to that specific antigen

CD8 cells eliminate antigen via **cell-mediated cytotoxicity** (see map)

mostly antigen is processed via class II MHC molecule

Th0 cells are activated and differentiate into **CD4 Th1** cells specific to that antigen

Effector Phase

Th1 cells clonally expand

2nd exposure to same antigen

Th1 cells secrete cytokines:
- **IFN** γ
- **TNF** α
- IL 8
- IL 2
- IL 3
- GM-CSF

recruits and activates mainly **macrophages** and other nonspecific inflammatory cells

inflammatory infiltrate arrives at site of infection 24 hours later = **delayed type hypersensitivity**

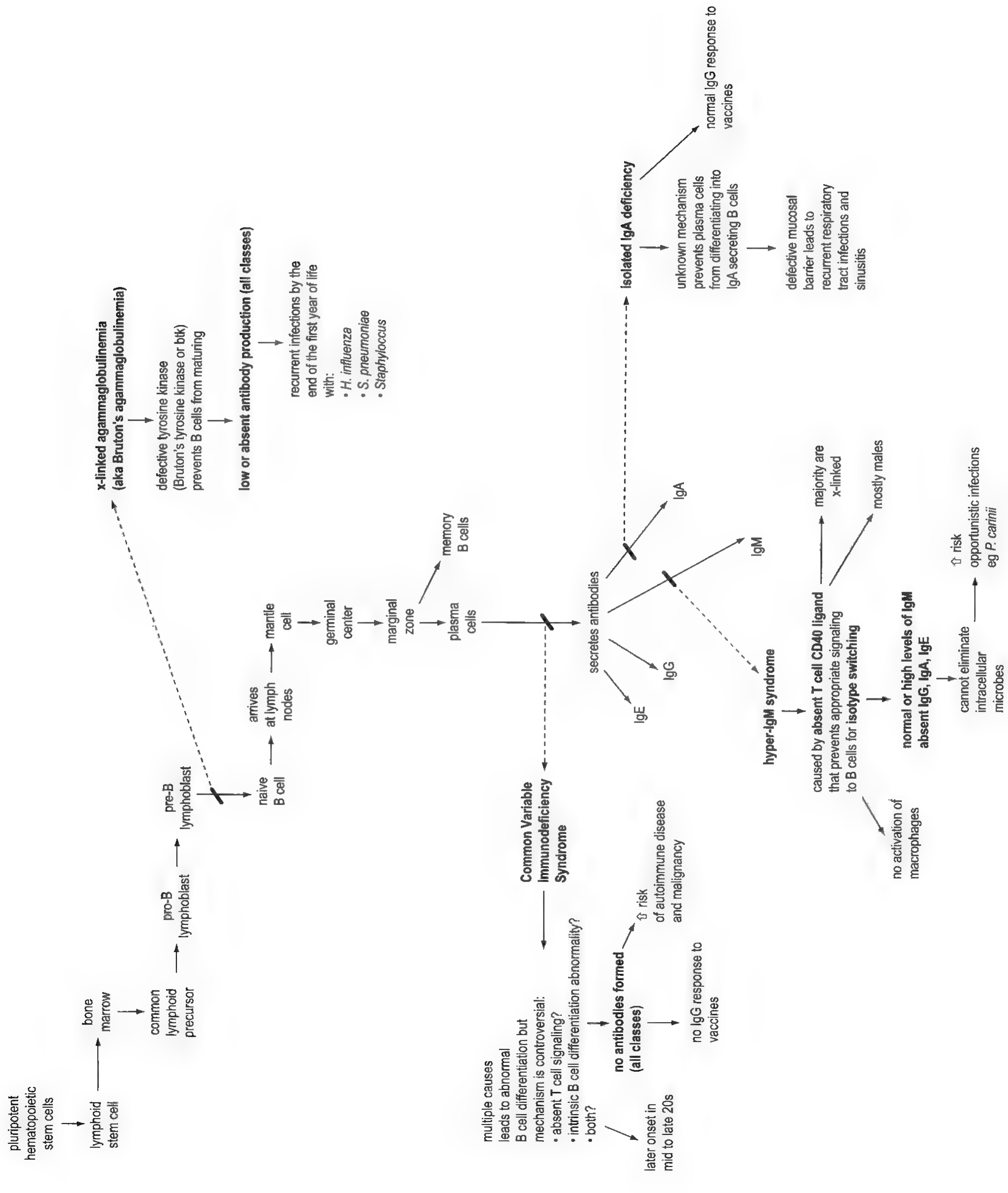
activated macrophages are responsible for most of the effects of the hypersensitivity reaction by:
- ⇧ phagocytosis
- ⇧ oxygen radical release
- ⇧ nitric oxide release

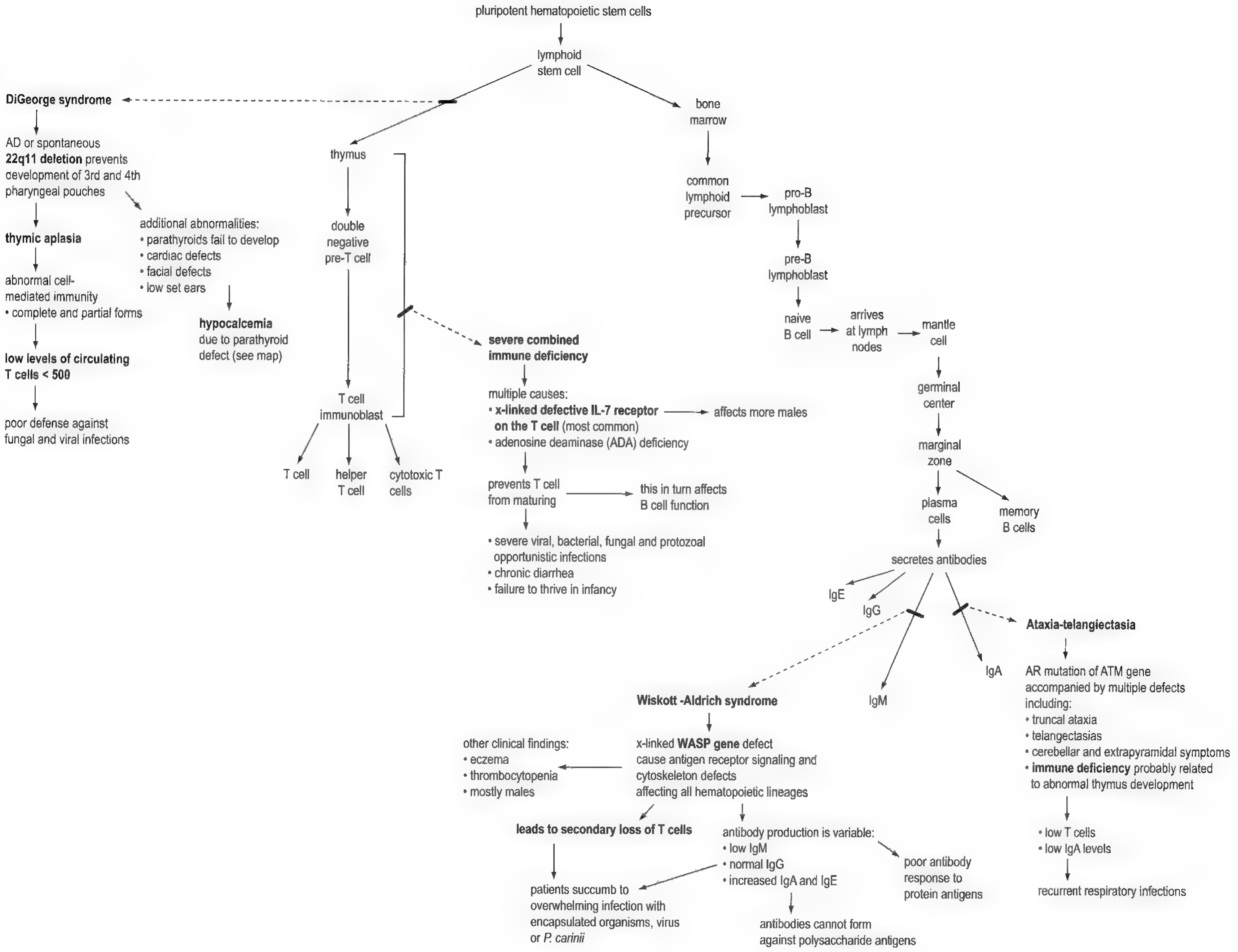
hypersensitivity response is further amplified by an increase in class II MHC molecule expression on activated macrophages

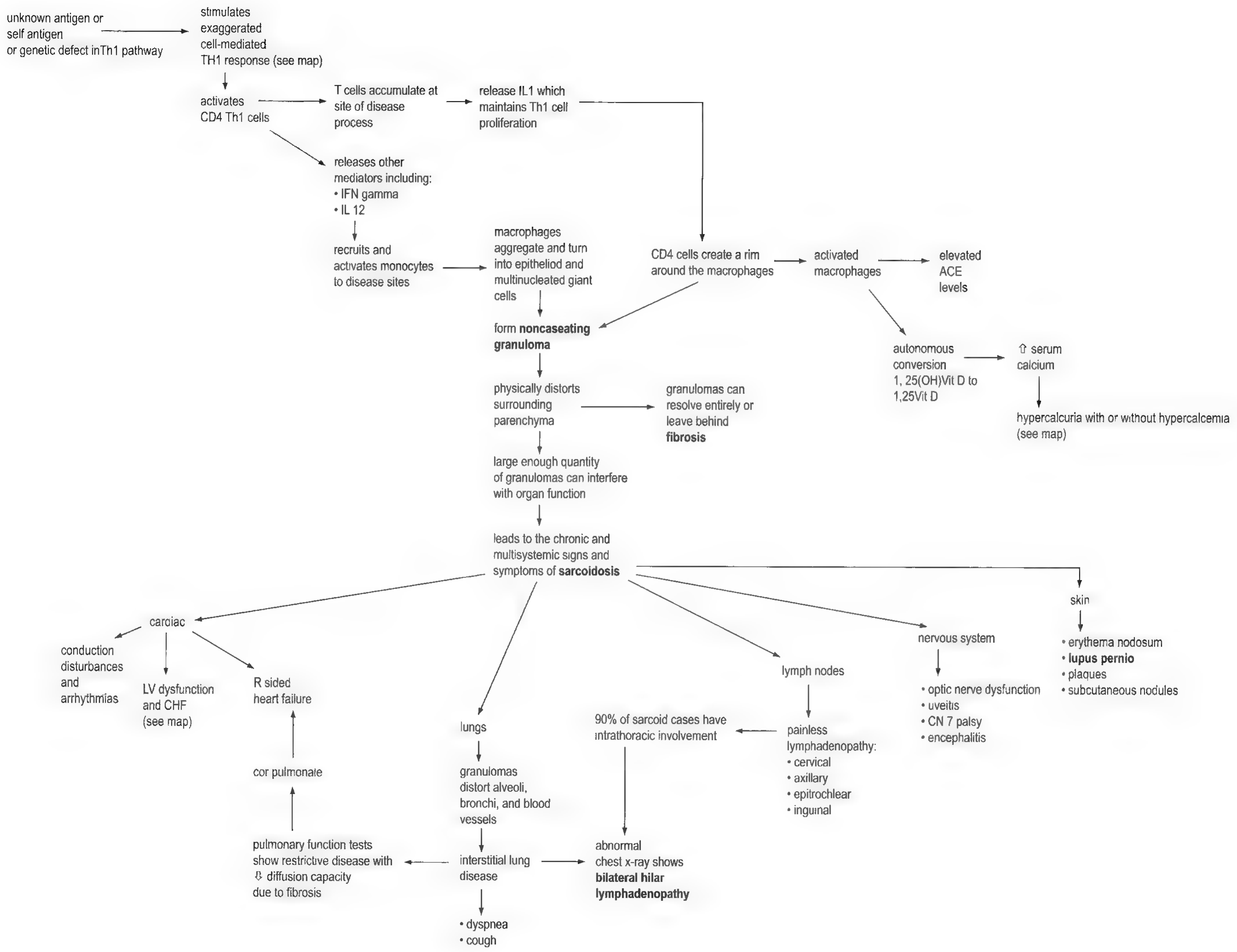
enables ⇧ antigen presentation

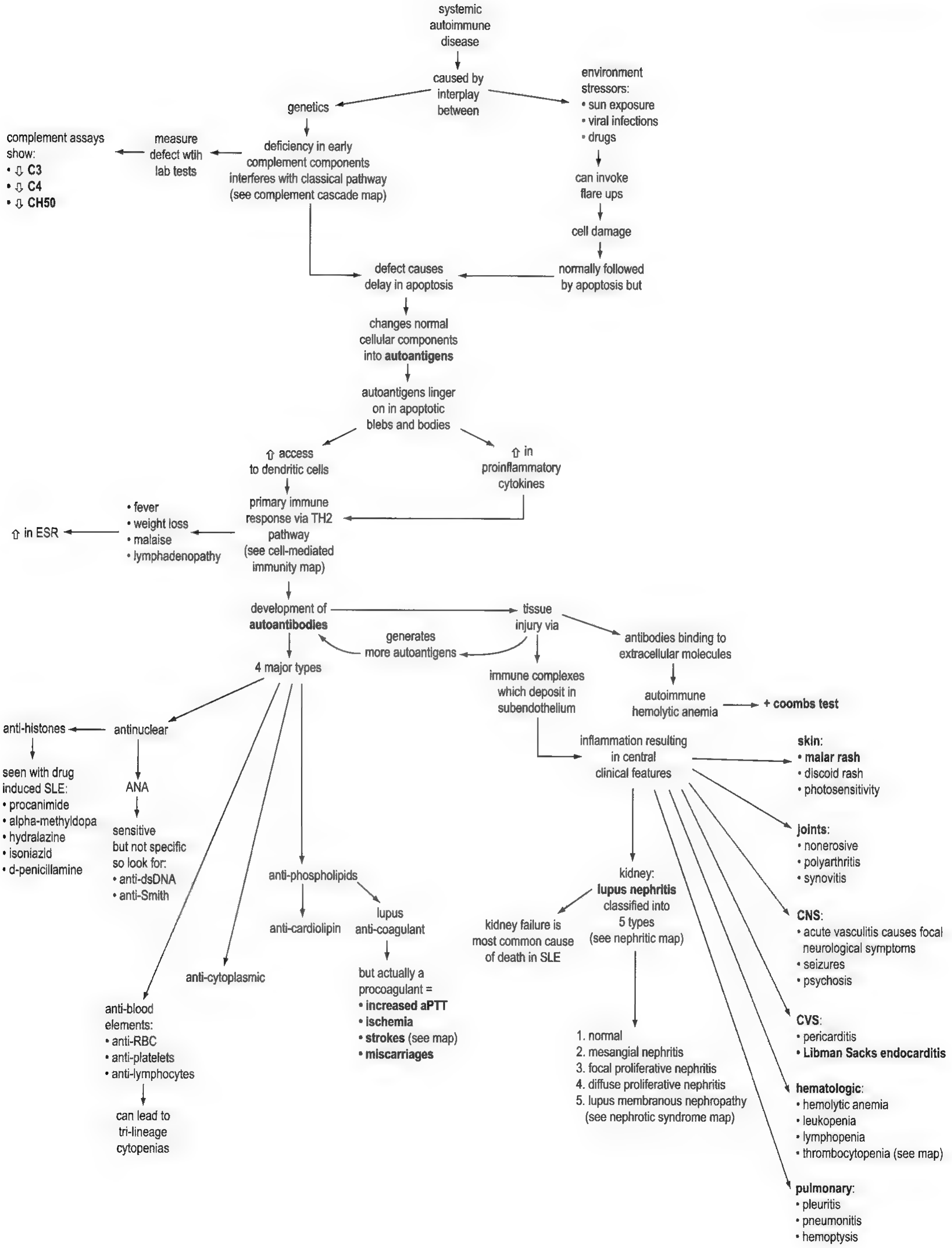
elimination of intracellular antigen occurs through **nonspecific destruction** of tissue

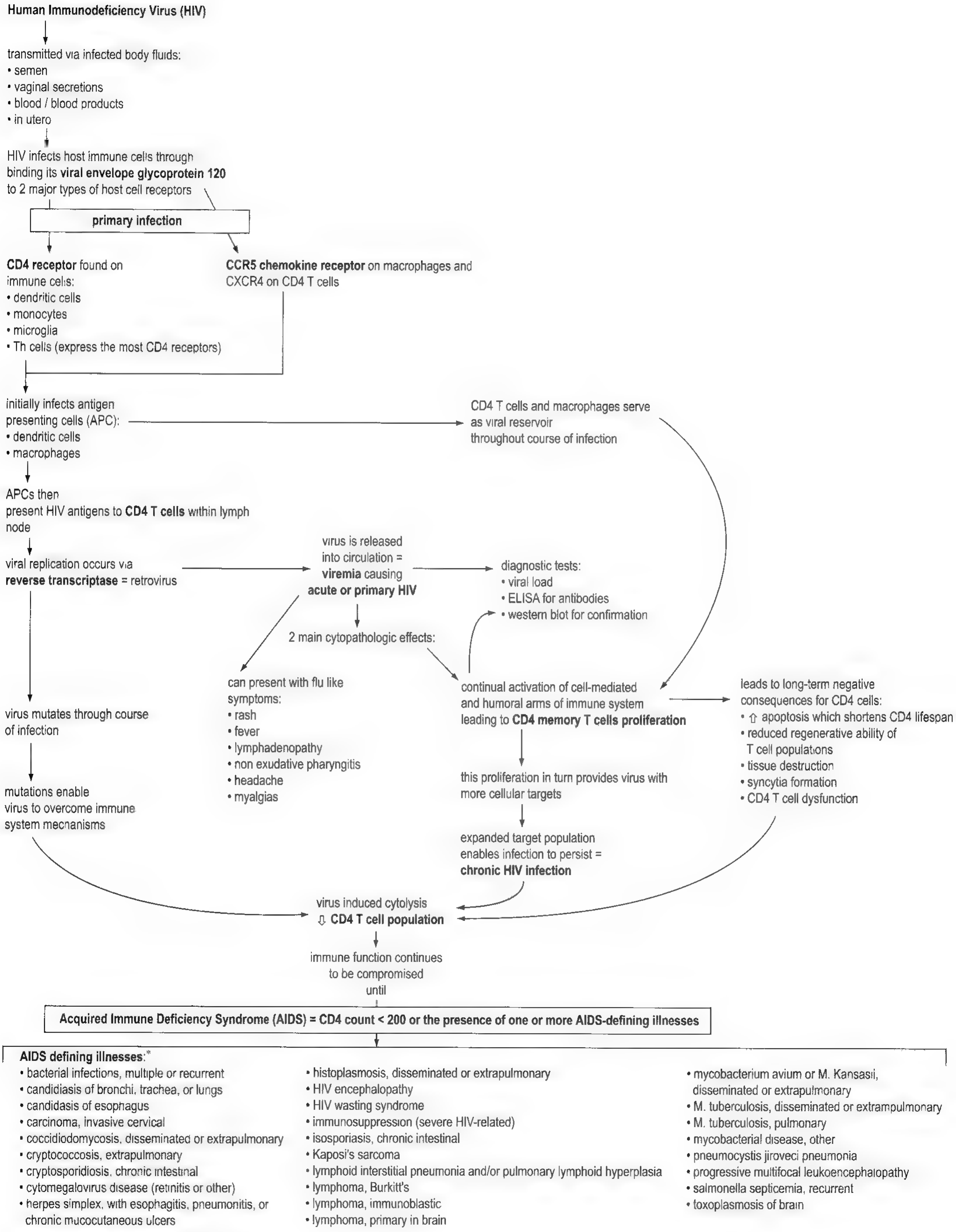
if hypersensitivity reaction is unable to eliminate antigen then continuous tissue damage can lead to **granulomatous reaction** (e.g. TB granulomas)


pluripotent hematopoietic stem cells
lymphoid stem cell
bone marrow
common lymphoid precursor
pro-B lymphoblast
pre-B lymphoblast
naive B cell
arrives at lymph nodes
mantle cell
germinal center
marginal zone
memory B cells
plasma cells
secretes antibodies
IgE
IgG
IgM
IgA
x-linked agammaglobulinemia (aka Bruton's agammaglobulinemia)
defective tyrosine kinase (Bruton's tyrosine kinase or btk) prevents B cells from maturing
low or absent antibody production (all classes)
recurrent infections by the end of the first year of life with:
• H. influenza
• S. pneumoniae
• Staphyloccus
isolated IgA deficiency
normal IgG response to vaccines
unknown mechanism prevents plasma cells from differentiating into IgA secreting B cells
defective mucosal barrier leads to recurrent respiratory tract infections and sinusitis
hyper-IgM syndrome
caused by absent T cell CD40 ligand that prevents appropriate signaling to B cells for isotype switching
majority are x-linked
mostly males
no activation of macrophages
normal or high levels of IgM absent IgG, IgA, IgE
cannot eliminate intracellular microbes
⇧ risk opportunistic infections eg P. carinii
Common Variable Immunodeficiency Syndrome
multiple causes leads to abnormal B cell differentiation but mechanism is controversial:
• absent T cell signaling?
• intrinsic B cell differentiation abnormality?
• both?
later onset in mid to late 20s
no antibodies formed (all classes)
⇧ risk of autoimmune disease and malignancy
no IgG response to vaccines


pluripotent hematopoietic stem cells
lymphoid stem cell
thymus
bone marrow
DiGeorge syndrome
AD or spontaneous **22q11 deletion** prevents development of 3rd and 4th pharyngeal pouches
additional abnormalities:
• parathyroids fail to develop
• cardiac defects
• facial defects
• low set ears
hypocalcemia due to parathyroid defect (see map)
thymic aplasia
abnormal cell-mediated immunity
• complete and partial forms
low levels of circulating T cells < 500
poor defense against fungal and viral infections
double negative pre-T cell
T cell immunoblast
T cell
helper T cell
cytotoxic T cells
severe combined immune deficiency
multiple causes:
• **x-linked defective IL-7 receptor on the T cell** (most common)
• adenosine deaminase (ADA) deficiency
affects more males
prevents T cell from maturing
this in turn affects B cell function
• severe viral, bacterial, fungal and protozoal opportunistic infections
• chronic diarrhea
• failure to thrive in infancy
common lymphoid precursor
pro-B lymphoblast
pre-B lymphoblast
naive B cell
arrives at lymph nodes
mantle cell
germinal center
marginal zone
plasma cells
memory B cells
secretes antibodies
IgE
IgG
IgM
IgA
Ataxia-telangiectasia
AR mutation of ATM gene accompanied by multiple defects including:
• truncal ataxia
• telangectasias
• cerebellar and extrapyramidal symptoms
• **immune deficiency** probably related to abnormal thymus development
• low T cells
• low IgA levels
recurrent respiratory infections
Wiskott -Aldrich syndrome
x-linked **WASP gene** defect cause antigen receptor signaling and cytoskeleton defects affecting all hematopoietic lineages
other clinical findings:
• eczema
• thrombocytopenia
• mostly males
leads to secondary loss of T cells
antibody production is variable:
• low IgM
• normal IgG
• increased IgA and IgE
poor antibody response to protein antigens
patients succumb to overwhelming infection with encapsulated organisms, virus or *P. carinii*
antibodies cannot form against polysaccharide antigens


unknown antigen or
self antigen
or genetic defect inTh1 pathway
stimulates
exaggerated
cell-mediated
TH1 response (see map)
activates
CD4 Th1 cells
T cells accumulate at
site of disease
process
release IL1 which
maintains Th1 cell
proliferation
releases other
mediators including:
• IFN gamma
• IL 12
recruits and
activates monocytes
to disease sites
macrophages
aggregate and turn
into epitheliod and
multinucleated giant
cells
CD4 cells create a rim
around the macrophages
activated
macrophages
elevated
ACE
levels
form **noncaseating**
granuloma
autonomous
conversion
1, 25(OH)Vit D to
1,25Vit D
⇧ serum
calcium
physically distorts
surrounding
parenchyma
granulomas can
resolve entirely or
leave behind
fibrosis
hypercalcuria with or without hypercalcemia
(see map)
large enough quantity
of granulomas can interfere
with organ function
leads to the chronic and
multisystemic signs and
symptoms of **sarcoidosis**
skin
cardiac
nervous system
• erythema nodosum
• **lupus pernio**
• plaques
• subcutaneous nodules
conduction
disturbances
and
arrhythmias
LV dysfunction
and CHF
(see map)
R sided
heart failure
lymph nodes
• optic nerve dysfunction
• uveitis
• CN 7 palsy
• encephalitis
lungs
90% of sarcoid cases have
intrathoracic involvement
painless
lymphadenopathy:
• cervical
• axillary
• epitrochlear
• inguinal
cor pulmonale
granulomas
distort alveoli,
bronchi, and blood
vessels
pulmonary function tests
show restrictive disease with
⇩ diffusion capacity
due to fibrosis
interstitial lung
disease
abnormal
chest x-ray shows
bilateral hilar
lymphadenopathy
• dyspnea
• cough


systemic autoimmune disease
caused by interplay between
genetics
environment stressors:
• sun exposure
• viral infections
• drugs
deficiency in early complement components interferes with classical pathway (see complement cascade map)
measure defect wtih lab tests
complement assays show:
• ⇩ **C3**
• ⇩ **C4**
• ⇩ **CH50**
can invoke flare ups
cell damage
normally followed by apoptosis but
defect causes delay in apoptosis
changes normal cellular components into **autoantigens**
autoantigens linger on in apoptotic blebs and bodies
⇧ access to dendritic cells
⇧ in proinflammatory cytokines
primary immune response via TH2 pathway (see cell-mediated immunity map)
• fever
• weight loss
• malaise
• lymphadenopathy
⇧ in ESR
development of **autoantibodies**
generates more autoantigens
tissue injury via
4 major types
immune complexes which deposit in subendothelium
antibodies binding to extracellular molecules
autoimmune hemolytic anemia
+ coombs test
antinuclear
anti-histones
seen with drug induced SLE:
• procanimide
• alpha-methyldopa
• hydralazine
• isoniazid
• d-penicillamine
ANA
sensitive but not specific so look for:
• anti-dsDNA
• anti-Smith
anti-phospholipids
anti-cardiolipin
lupus anti-coagulant
but actually a procoagulant =
• **increased aPTT**
• **ischemia**
• **strokes** (see map)
• **miscarriages**
anti-cytoplasmic
anti-blood elements:
• anti-RBC
• anti-platelets
• anti-lymphocytes
can lead to tri-lineage cytopenias
inflammation resulting in central clinical features
skin:
• **malar rash**
• discoid rash
• photosensitivity
joints:
• nonerosive
• polyarthritis
• synovitis
CNS:
• acute vasculitis causes focal neurological symptoms
• seizures
• psychosis
CVS:
• pericarditis
• **Libman Sacks endocarditis**
hematologic:
• hemolytic anemia
• leukopenia
• lymphopenia
• thrombocytopenia (see map)
pulmonary:
• pleuritis
• pneumonitis
• hemoptysis
kidney: **lupus nephritis** classified into 5 types (see nephritic map)
kidney failure is most common cause of death in SLE
1. normal
2. mesangial nephritis
3. focal proliferative nephritis
4. diffuse proliferative nephritis
5. lupus membranous nephropathy (see nephrotic syndrome map)



Human Immunodeficiency Virus (HIV)

transmitted via infected body fluids:
- semen
- vaginal secretions
- blood / blood products
- in utero

HIV infects host immune cells through binding its **viral envelope glycoprotein 120** to 2 major types of host cell receptors

primary infection

CD4 receptor found on immune cells:
- dendritic cells
- monocytes
- microglia
- Th cells (express the most CD4 receptors)

CCR5 chemokine receptor on macrophages and CXCR4 on CD4 T cells

initially infects antigen presenting cells (APC):
- dendritic cells
- macrophages

CD4 T cells and macrophages serve as viral reservoir throughout course of infection

APCs then present HIV antigens to **CD4 T cells** within lymph node

viral replication occurs via **reverse transcriptase** = retrovirus

virus is released into circulation = **viremia** causing **acute or primary HIV**

diagnostic tests:
- viral load
- ELISA for antibodies
- western blot for confirmation

2 main cytopathologic effects:

can present with flu like symptoms:
- rash
- fever
- lymphadenopathy
- non exudative pharyngitis
- headache
- myalgias

continual activation of cell-mediated and humoral arms of immune system leading to **CD4 memory T cells proliferation**

leads to long-term negative consequences for CD4 cells:
- ⇧ apoptosis which shortens CD4 lifespan
- reduced regenerative ability of T cell populations
- tissue destruction
- syncytia formation
- CD4 T cell dysfunction

this proliferation in turn provides virus with more cellular targets

expanded target population enables infection to persist = **chronic HIV infection**

virus mutates through course of infection

mutations enable virus to overcome immune system mechanisms

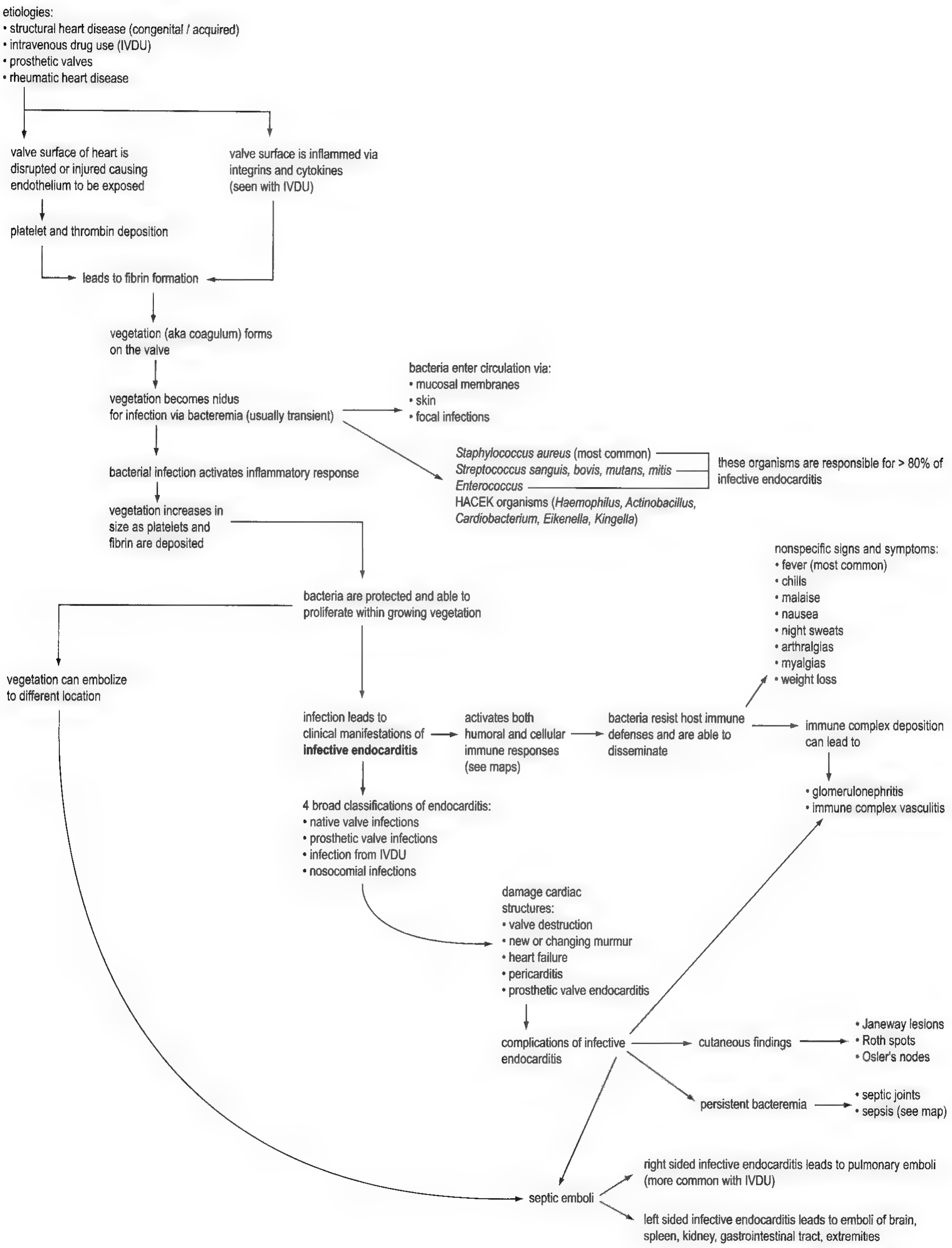
virus induced cytolysis
⇩ **CD4 T cell population**

immune function continues to be compromised until

Acquired Immune Deficiency Syndrome (AIDS) = CD4 count < 200 or the presence of one or more AIDS-defining illnesses

AIDS defining illnesses:*
- bacterial infections, multiple or recurrent
- candidiasis of bronchi, trachea, or lungs
- candidasis of esophagus
- carcinoma, invasive cervical
- coccidiodomycosis, disseminated or extrapulmonary
- cryptococcosis, extrapulmonary
- cryptosporidiosis, chronic intestinal
- cytomegalovirus disease (retinitis or other)
- herpes simplex, with esophagitis, pneumonitis, or chronic mucocutaneous ulcers
- histoplasmosis, disseminated or extrapulmonary
- HIV encephalopathy
- HIV wasting syndrome
- immunosuppression (severe HIV-related)
- isosporiasis, chronic intestinal
- Kaposi's sarcoma
- lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia
- lymphoma, Burkitt's
- lymphoma, immunoblastic
- lymphoma, primary in brain
- mycobacterium avium or M. Kansasii, disseminated or extrapulmonary
- M. tuberculosis, disseminated or extrampulmonary
- M. tuberculosis, pulmonary
- mycobacterial disease, other
- pneumocystis jiroveci pneumonia
- progressive multifocal leukoencephalopathy
- salmonella septicemia, recurrent
- toxoplasmosis of brain

*CDC's AIDS surveillance case definition conditions.



etiologies:
- structural heart disease (congenital / acquired)
- intravenous drug use (IVDU)
- prosthetic valves
- rheumatic heart disease

valve surface of heart is disrupted or injured causing endothelium to be exposed

platelet and thrombin deposition

valve surface is inflammed via integrins and cytokines (seen with IVDU)

leads to fibrin formation

vegetation (aka coagulum) forms on the valve

vegetation becomes nidus for infection via bacteremia (usually transient)

bacteria enter circulation via:
- mucosal membranes
- skin
- focal infections

Staphylococcus aureus (most common)
Streptococcus sanguis, bovis, mutans, mitis
Enterococcus
HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)

these organisms are responsible for > 80% of infective endocarditis

bacterial infection activates inflammatory response

vegetation increases in size as platelets and fibrin are deposited

bacteria are protected and able to proliferate within growing vegetation

vegetation can embolize to different location

infection leads to clinical manifestations of **infective endocarditis**

activates both humoral and cellular immune responses (see maps)

bacteria resist host immune defenses and are able to disseminate

nonspecific signs and symptoms:
- fever (most common)
- chills
- malaise
- nausea
- night sweats
- arthralgias
- myalgias
- weight loss

immune complex deposition can lead to
- glomerulonephritis
- immune complex vasculitis

4 broad classifications of endocarditis:
- native valve infections
- prosthetic valve infections
- infection from IVDU
- nosocomial infections

damage cardiac structures:
- valve destruction
- new or changing murmur
- heart failure
- pericarditis
- prosthetic valve endocarditis

complications of infective endocarditis

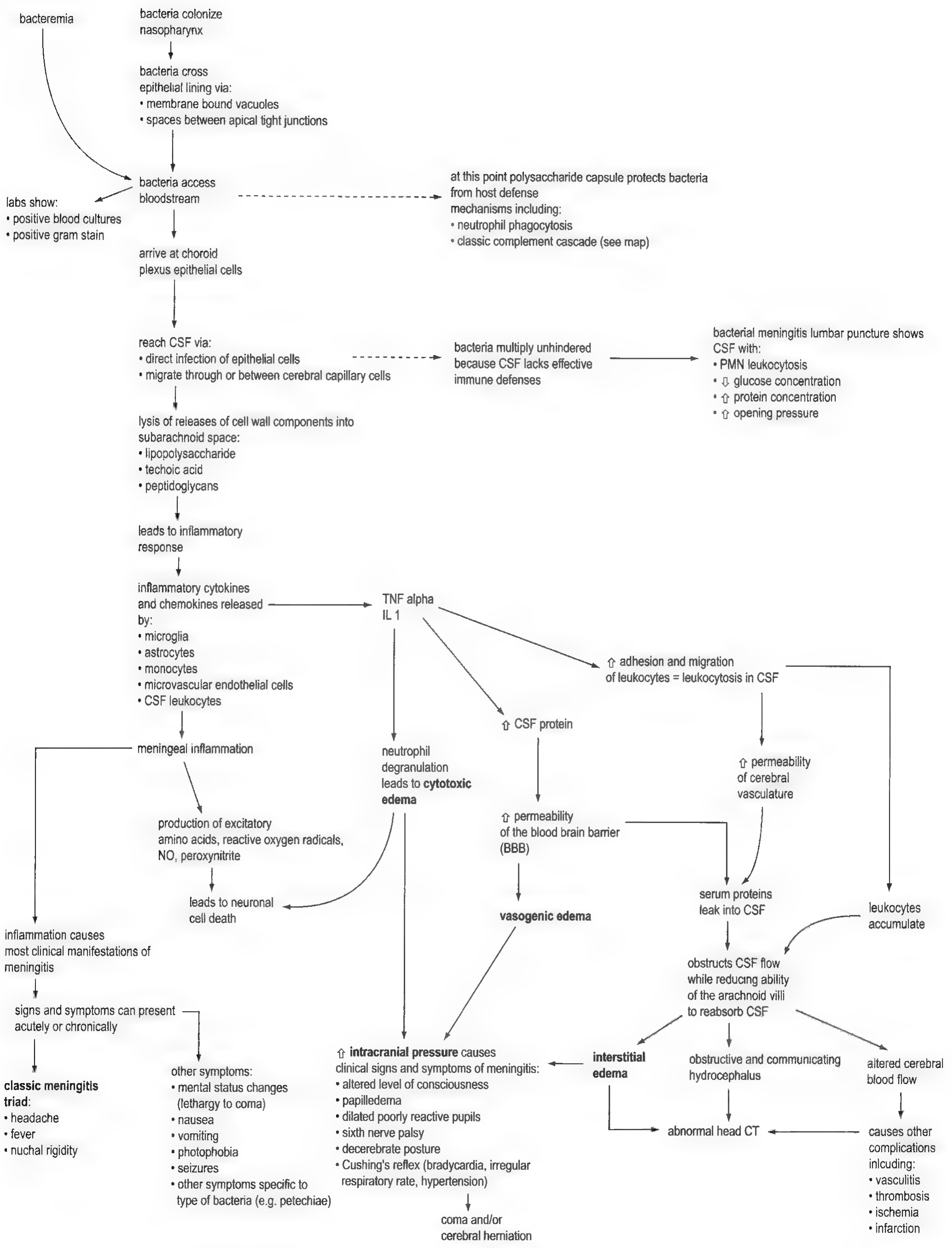
cutaneous findings
- Janeway lesions
- Roth spots
- Osler's nodes

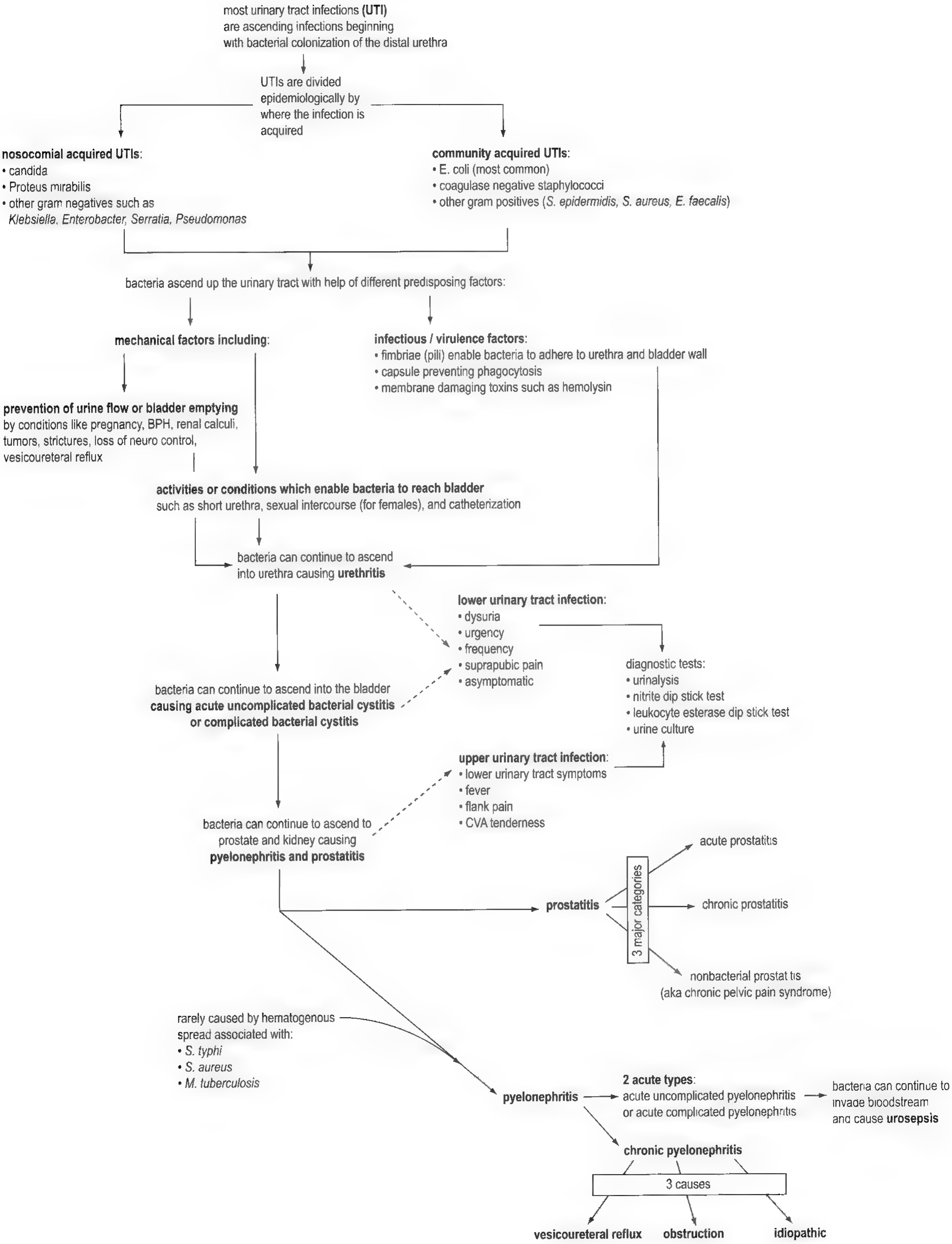
persistent bacteremia
- septic joints
- sepsis (see map)

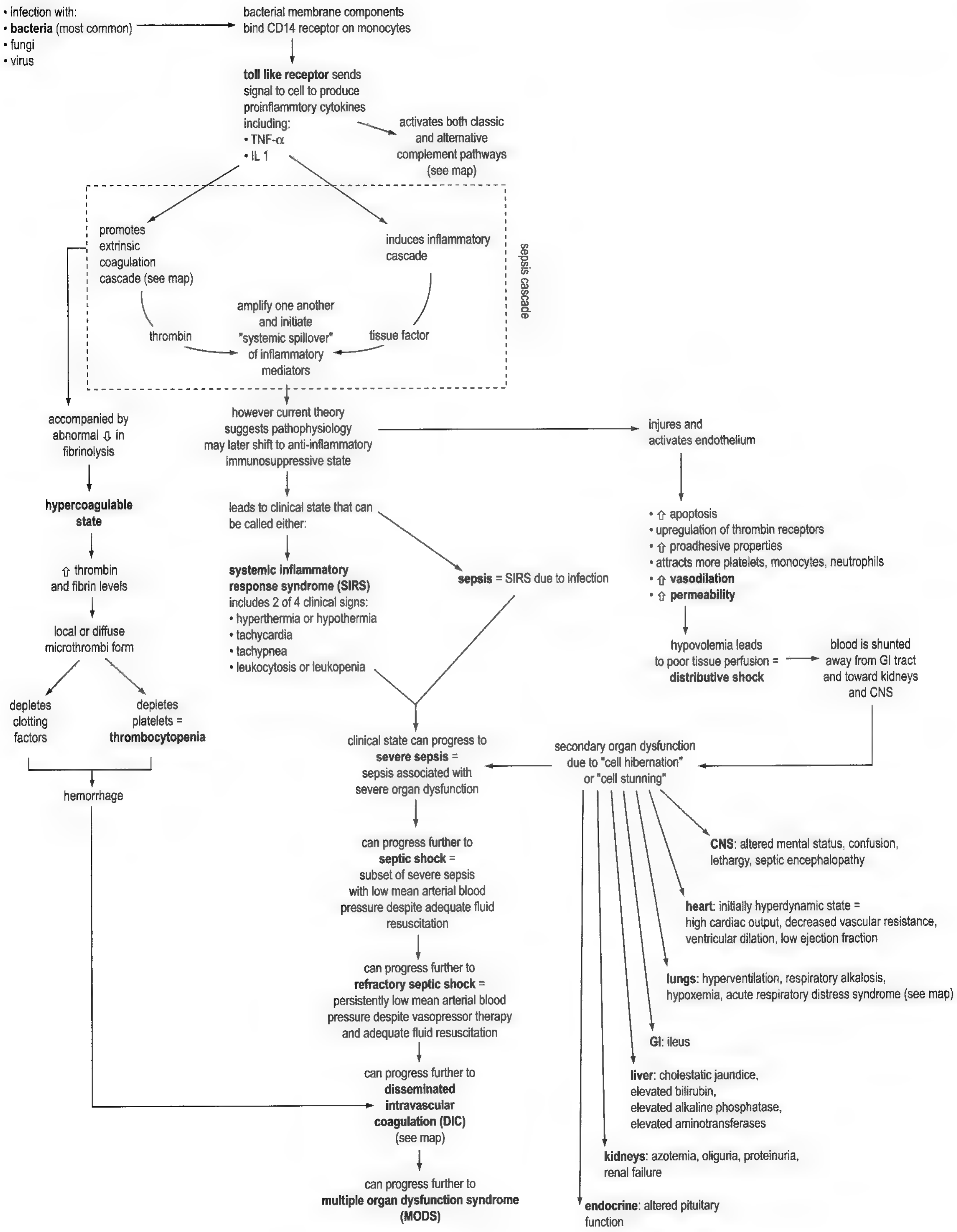
septic emboli

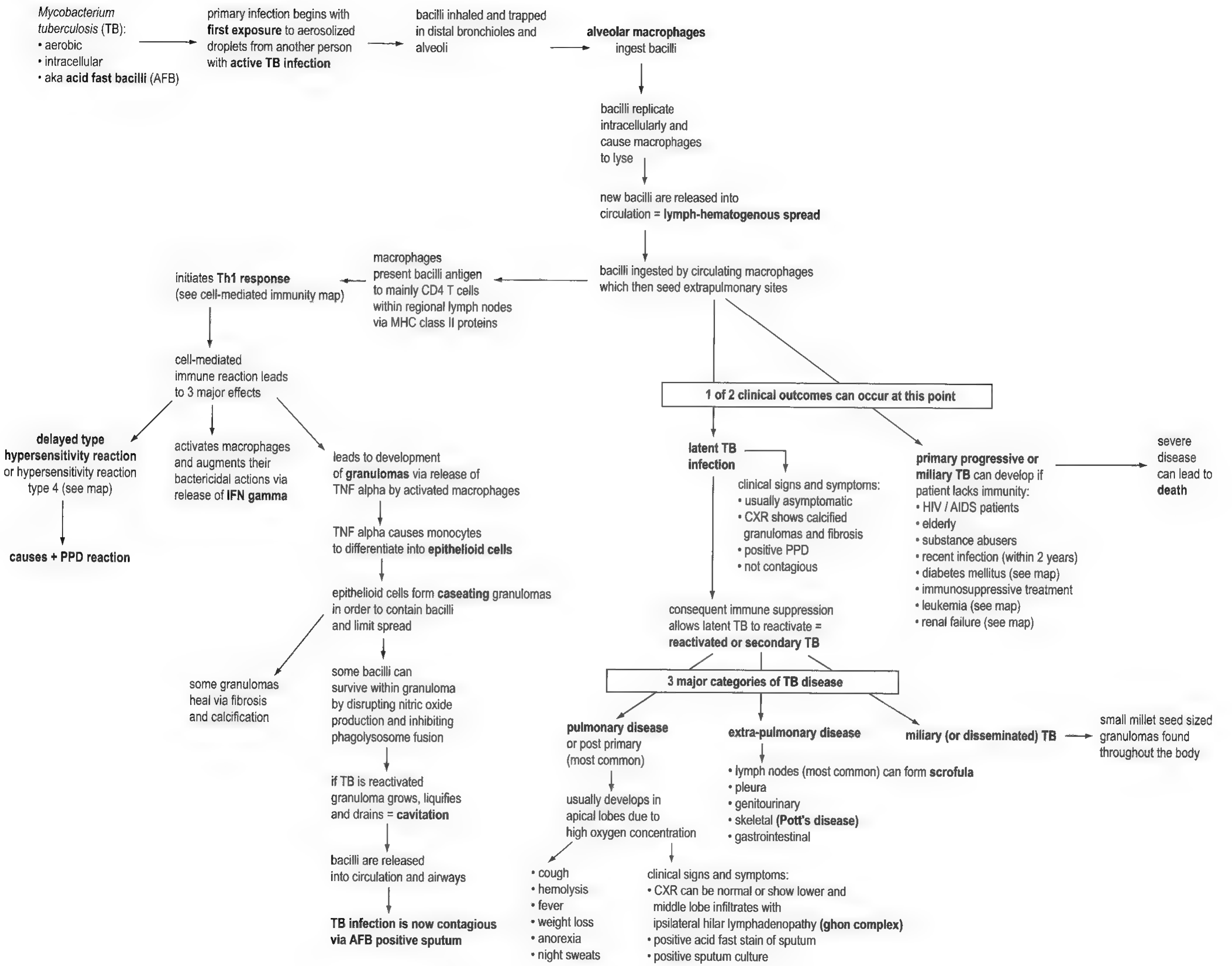
right sided infective endocarditis leads to pulmonary emboli (more common with IVDU)

left sided infective endocarditis leads to emboli of brain, spleen, kidney, gastrointestinal tract, extremities


bacteremia
bacteria colonize nasopharynx
bacteria cross epithelial lining via:
• membrane bound vacuoles
• spaces between apical tight junctions
bacteria access bloodstream
labs show:
• positive blood cultures
• positive gram stain
at this point polysaccharide capsule protects bacteria from host defense mechanisms including:
• neutrophil phagocytosis
• classic complement cascade (see map)
arrive at choroid plexus epithelial cells
reach CSF via:
• direct infection of epithelial cells
• migrate through or between cerebral capillary cells
bacteria multiply unhindered because CSF lacks effective immune defenses
bacterial meningitis lumbar puncture shows CSF with:
• PMN leukocytosis
• ⇩ glucose concentration
• ⇧ protein concentration
• ⇧ opening pressure
lysis of releases of cell wall components into subarachnoid space:
• lipopolysaccharide
• techoic acid
• peptidoglycans
leads to inflammatory response
inflammatory cytokines and chemokines released by:
• microglia
• astrocytes
• monocytes
• microvascular endothelial cells
• CSF leukocytes
TNF alpha
IL 1
⇧ adhesion and migration of leukocytes = leukocytosis in CSF
⇧ CSF protein
meningeal inflammation
neutrophil degranulation leads to **cytotoxic edema**
⇧ permeability of cerebral vasculature
production of excitatory amino acids, reactive oxygen radicals, NO, peroxynitrite
⇧ permeability of the blood brain barrier (BBB)
leads to neuronal cell death
vasogenic edema
serum proteins leak into CSF
leukocytes accumulate
inflammation causes most clinical manifestations of meningitis
obstructs CSF flow while reducing ability of the arachnoid villi to reabsorb CSF
signs and symptoms can present acutely or chronically
classic meningitis triad:
• headache
• fever
• nuchal rigidity
other symptoms:
• mental status changes (lethargy to coma)
• nausea
• vomiting
• photophobia
• seizures
• other symptoms specific to type of bacteria (e.g. petechiae)
⇧ **intracranial pressure** causes clinical signs and symptoms of meningitis:
• altered level of consciousness
• papilledema
• dilated poorly reactive pupils
• sixth nerve palsy
• decerebrate posture
• Cushing's reflex (bradycardia, irregular respiratory rate, hypertension)
coma and/or cerebral herniation
interstitial edema
obstructive and communicating hydrocephalus
altered cerebral blood flow
abnormal head CT
causes other complications inlcuding:
• vasculitis
• thrombosis
• ischemia
• infarction


most urinary tract infections **(UTI)** are ascending infections beginning with bacterial colonization of the distal urethra
UTIs are divided epidemiologically by where the infection is acquired
nosocomial acquired UTIs:
• candida
• Proteus mirabilis
• other gram negatives such as *Klebsiella, Enterobacter, Serratia, Pseudomonas*
community acquired UTIs:
• E. coli (most common)
• coagulase negative staphylococci
• other gram positives (*S. epidermidis, S. aureus, E. faecalis*)
bacteria ascend up the urinary tract with help of different predisposing factors:
mechanical factors including:
infectious / virulence factors:
• fimbriae (pili) enable bacteria to adhere to urethra and bladder wall
• capsule preventing phagocytosis
• membrane damaging toxins such as hemolysin
prevention of urine flow or bladder emptying by conditions like pregnancy, BPH, renal calculi, tumors, strictures, loss of neuro control, vesicoureteral reflux
activities or conditions which enable bacteria to reach bladder such as short urethra, sexual intercourse (for females), and catheterization
bacteria can continue to ascend into urethra causing **urethritis**
lower urinary tract infection:
• dysuria
• urgency
• frequency
• suprapubic pain
• asymptomatic
diagnostic tests:
• urinalysis
• nitrite dip stick test
• leukocyte esterase dip stick test
• urine culture
bacteria can continue to ascend into the bladder **causing acute uncomplicated bacterial cystitis or complicated bacterial cystitis**
upper urinary tract infection:
• lower urinary tract symptoms
• fever
• flank pain
• CVA tenderness
bacteria can continue to ascend to prostate and kidney causing **pyelonephritis and prostatitis**
prostatitis
3 major categories
acute prostatitis
chronic prostatitis
nonbacterial prostatitis (aka chronic pelvic pain syndrome)
rarely caused by hematogenous spread associated with:
• *S. typhi*
• *S. aureus*
• *M. tuberculosis*
pyelonephritis
2 acute types: acute uncomplicated pyelonephritis or acute complicated pyelonephritis
bacteria can continue to invade bloodstream and cause **urosepsis**
chronic pyelonephritis
3 causes
vesicoureteral reflux
obstruction
idiopathic


• infection with:
• bacteria (most common)
• fungi
• virus
bacterial membrane components bind CD14 receptor on monocytes
toll like receptor sends signal to cell to produce proinflammtory cytokines including:
• TNF-α
• IL 1
activates both classic and alternative complement pathways (see map)
sepsis cascade
promotes extrinsic coagulation cascade (see map)
induces inflammatory cascade
thrombin
tissue factor
amplify one another and initiate "systemic spillover" of inflammatory mediators
accompanied by abnormal ⇩ in fibrinolysis
hypercoagulable state
⇧ thrombin and fibrin levels
local or diffuse microthrombi form
depletes clotting factors
depletes platelets = thrombocytopenia
hemorrhage
however current theory suggests pathophysiology may later shift to anti-inflammatory immunosuppressive state
leads to clinical state that can be called either:
systemic inflammatory response syndrome (SIRS) includes 2 of 4 clinical signs:
• hyperthermia or hypothermia
• tachycardia
• tachypnea
• leukocytosis or leukopenia
sepsis = SIRS due to infection
clinical state can progress to severe sepsis = sepsis associated with severe organ dysfunction
can progress further to septic shock = subset of severe sepsis with low mean arterial blood pressure despite adequate fluid resuscitation
can progress further to refractory septic shock = persistently low mean arterial blood pressure despite vasopressor therapy and adequate fluid resuscitation
can progress further to disseminated intravascular coagulation (DIC) (see map)
can progress further to multiple organ dysfunction syndrome (MODS)
injures and activates endothelium
• ⇧ apoptosis
• upregulation of thrombin receptors
• ⇧ proadhesive properties
• attracts more platelets, monocytes, neutrophils
• ⇧ vasodilation
• ⇧ permeability
hypovolemia leads to poor tissue perfusion = distributive shock
blood is shunted away from GI tract and toward kidneys and CNS
secondary organ dysfunction due to "cell hibernation" or "cell stunning"
CNS: altered mental status, confusion, lethargy, septic encephalopathy
heart: initially hyperdynamic state = high cardiac output, decreased vascular resistance, ventricular dilation, low ejection fraction
lungs: hyperventilation, respiratory alkalosis, hypoxemia, acute respiratory distress syndrome (see map)
GI: ileus
liver: cholestatic jaundice, elevated bilirubin, elevated alkaline phosphatase, elevated aminotransferases
kidneys: azotemia, oliguria, proteinuria, renal failure
endocrine: altered pituitary function



Mycobacterium tuberculosis (TB):
- aerobic
- intracellular
- aka **acid fast bacilli** (AFB)

primary infection begins with **first exposure** to aerosolized droplets from another person with **active TB infection**

bacilli inhaled and trapped in distal bronchioles and alveoli

alveolar macrophages ingest bacilli

bacilli replicate intracellularly and cause macrophages to lyse

new bacilli are released into circulation = **lymph-hematogenous spread**

bacilli ingested by circulating macrophages which then seed extrapulmonary sites

macrophages present bacilli antigen to mainly CD4 T cells within regional lymph nodes via MHC class II proteins

initiates **Th1 response** (see cell-mediated immunity map)

cell-mediated immune reaction leads to 3 major effects

delayed type hypersensitivity reaction or hypersensitivity reaction type 4 (see map)

causes + PPD reaction

activates macrophages and augments their bactericidal actions via release of **IFN gamma**

leads to development of **granulomas** via release of TNF alpha by activated macrophages

TNF alpha causes monocytes to differentiate into **epithelioid cells**

epithelioid cells form **caseating** granulomas in order to contain bacilli and limit spread

some granulomas heal via fibrosis and calcification

some bacilli can survive within granuloma by disrupting nitric oxide production and inhibiting phagolysosome fusion

if TB is reactivated granuloma grows, liquifies and drains = **cavitation**

bacilli are released into circulation and airways

TB infection is now contagious via AFB positive sputum

1 of 2 clinical outcomes can occur at this point

latent TB infection

clinical signs and symptoms:
- usually asymptomatic
- CXR shows calcified granulomas and fibrosis
- positive PPD
- not contagious

consequent immune suppression allows latent TB to reactivate = **reactivated or secondary TB**

primary progressive or miliary TB can develop if patient lacks immunity:
- HIV / AIDS patients
- elderly
- substance abusers
- recent infection (within 2 years)
- diabetes mellitus (see map)
- immunosuppressive treatment
- leukemia (see map)
- renal failure (see map)

severe disease can lead to **death**

3 major categories of TB disease

pulmonary disease or post primary (most common)

usually develops in apical lobes due to high oxygen concentration

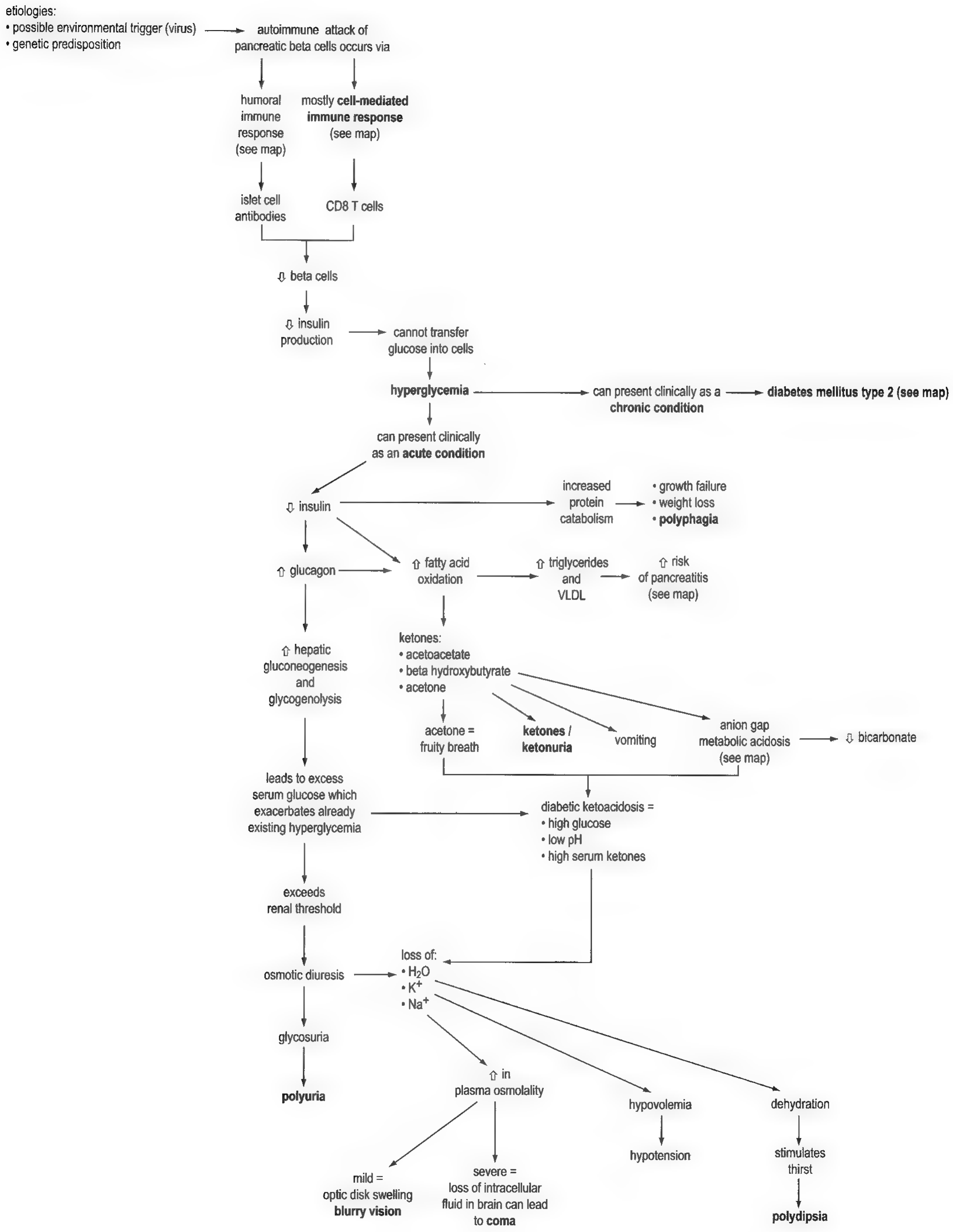
- cough
- hemolysis
- fever
- weight loss
- anorexia
- night sweats

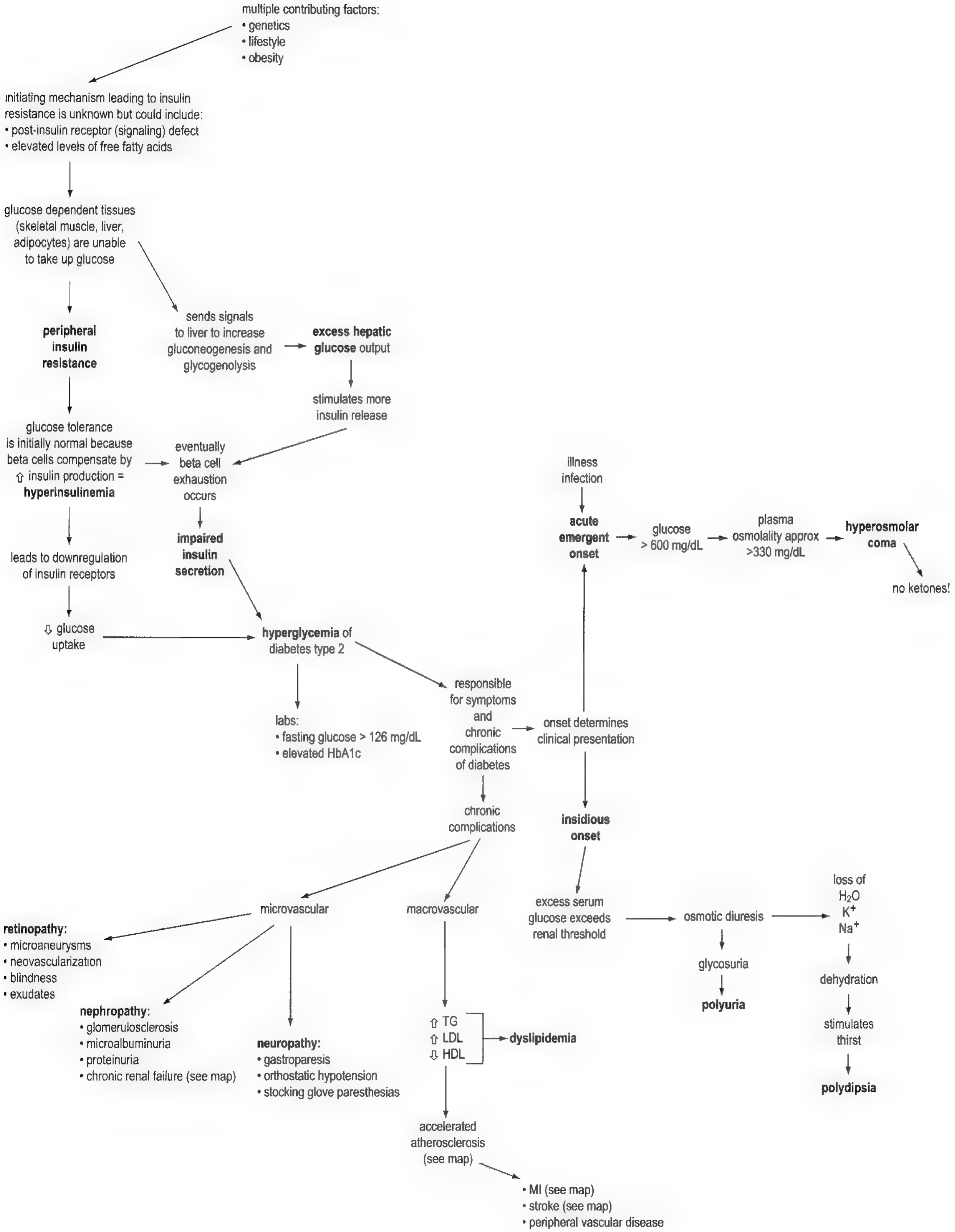
clinical signs and symptoms:
- CXR can be normal or show lower and middle lobe infiltrates with ipsilateral hilar lymphadenopathy **(ghon complex)**
- positive acid fast stain of sputum
- positive sputum culture

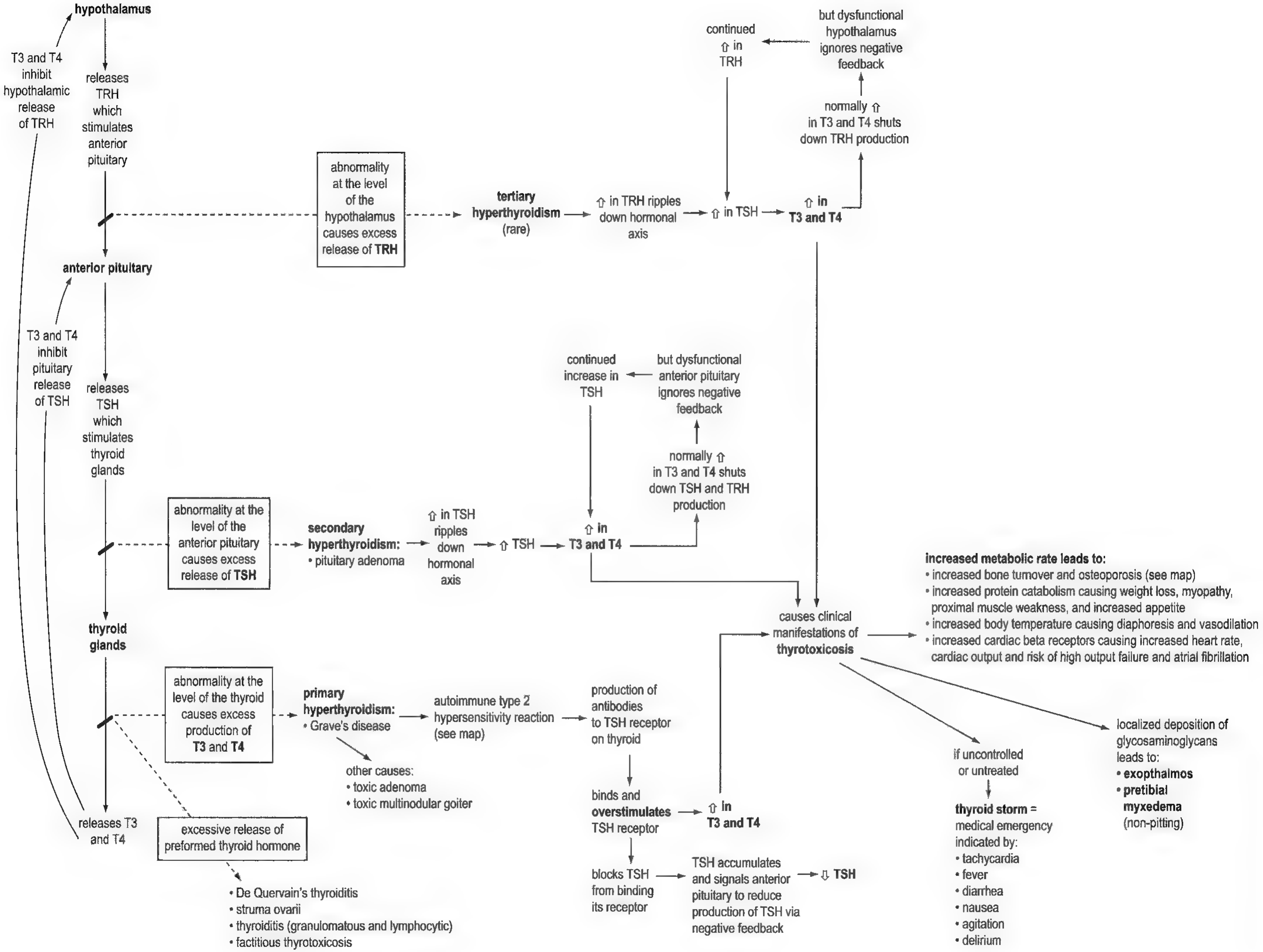
extra-pulmonary disease
- lymph nodes (most common) can form **scrofula**
- pleura
- genitourinary
- skeletal **(Pott's disease)**
- gastrointestinal

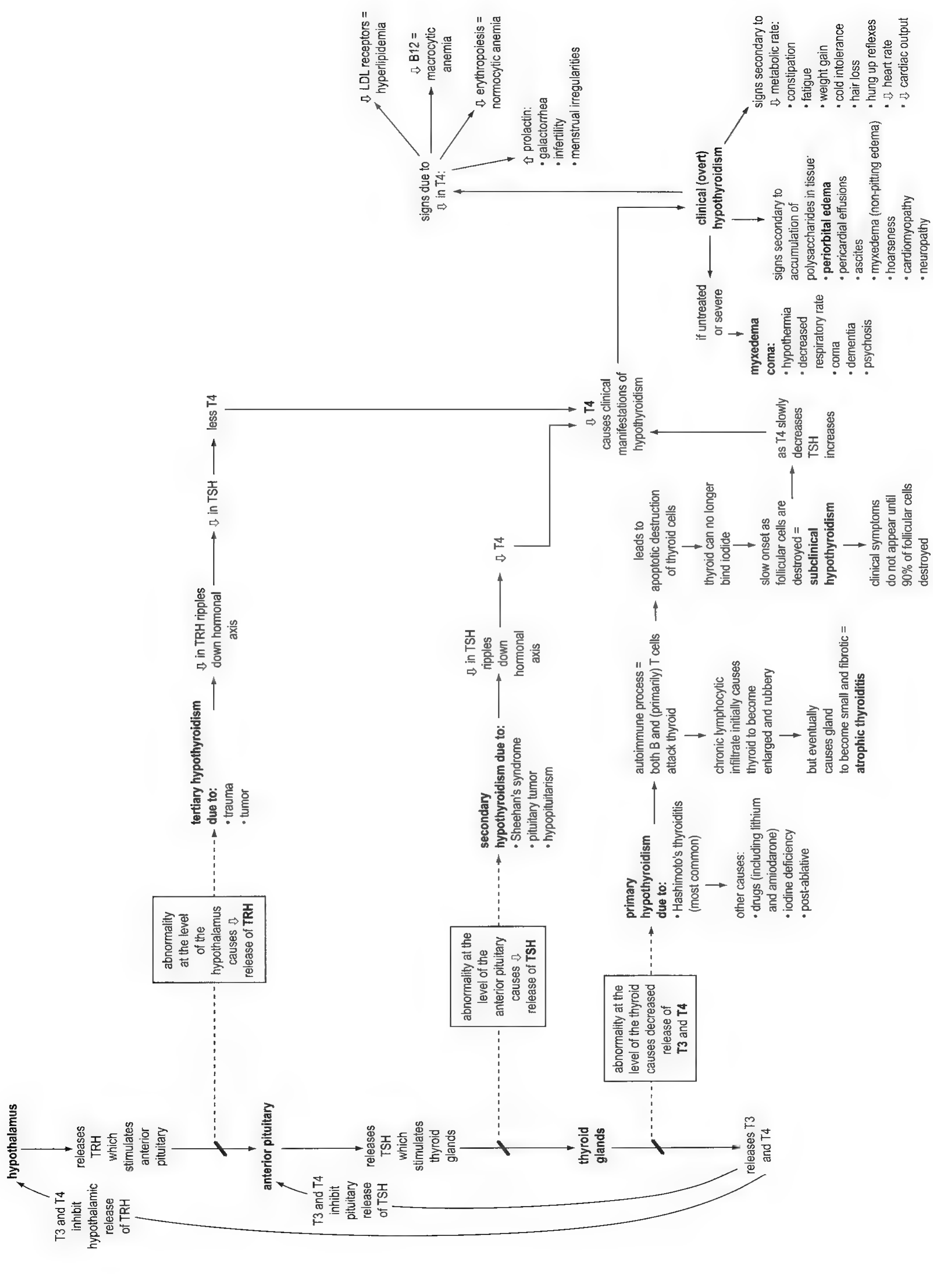
miliary (or disseminated) TB

small millet seed sized granulomas found throughout the body


etiologies:
• possible environmental trigger (virus)
• genetic predisposition
autoimmune attack of pancreatic beta cells occurs via
humoral immune response (see map)
mostly **cell-mediated immune response** (see map)
islet cell antibodies
CD8 T cells
⇩ beta cells
⇩ insulin production
cannot transfer glucose into cells
hyperglycemia
can present clinically as a **chronic condition**
diabetes mellitus type 2 (see map)
can present clinically as an **acute condition**
⇩ insulin
increased protein catabolism
• growth failure
• weight loss
• **polyphagia**
⇧ glucagon
⇧ fatty acid oxidation
⇧ triglycerides and VLDL
⇧ risk of pancreatitis (see map)
⇧ hepatic gluconeogenesis and glycogenolysis
ketones:
• acetoacetate
• beta hydroxybutyrate
• acetone
acetone = fruity breath
ketones / ketonuria
vomiting
anion gap metabolic acidosis (see map)
⇩ bicarbonate
leads to excess serum glucose which exacerbates already existing hyperglycemia
diabetic ketoacidosis =
• high glucose
• low pH
• high serum ketones
exceeds renal threshold
osmotic diuresis
loss of:
• H_2O
• K^+
• Na^+
glycosuria
polyuria
⇧ in plasma osmolality
hypovolemia
dehydration
hypotension
stimulates thirst
polydipsia
mild = optic disk swelling **blurry vision**
severe = loss of intracellular fluid in brain can lead to **coma**


multiple contributing factors:
• genetics
• lifestyle
• obesity
initiating mechanism leading to insulin resistance is unknown but could include:
• post-insulin receptor (signaling) defect
• elevated levels of free fatty acids
glucose dependent tissues (skeletal muscle, liver, adipocytes) are unable to take up glucose
peripheral insulin resistance
sends signals to liver to increase gluconeogenesis and glycogenolysis
excess hepatic glucose output
stimulates more insulin release
glucose tolerance is initially normal because beta cells compensate by ⇧ insulin production = **hyperinsulinemia**
eventually beta cell exhaustion occurs
impaired insulin secretion
leads to downregulation of insulin receptors
⇩ glucose uptake
hyperglycemia of diabetes type 2
labs:
• fasting glucose > 126 mg/dL
• elevated HbA1c
responsible for symptoms and chronic complications of diabetes
onset determines clinical presentation
illness
infection
acute emergent onset
glucose > 600 mg/dL
plasma osmolality approx >330 mg/dL
hyperosmolar coma
no ketones!
insidious onset
chronic complications
microvascular
macrovascular
retinopathy:
• microaneurysms
• neovascularization
• blindness
• exudates
nephropathy:
• glomerulosclerosis
• microalbuminuria
• proteinuria
• chronic renal failure (see map)
neuropathy:
• gastroparesis
• orthostatic hypotension
• stocking glove paresthesias
⇧ TG
⇧ LDL
⇩ HDL
dyslipidemia
accelerated atherosclerosis (see map)
• MI (see map)
• stroke (see map)
• peripheral vascular disease
excess serum glucose exceeds renal threshold
osmotic diuresis
glycosuria
polyuria
loss of H_2O K^+ Na^+
dehydration
stimulates thirst
polydipsia


hypothalamus
releases TRH which stimulates anterior pituitary
T3 and T4 inhibit hypothalamic release of TRH
anterior pituitary
releases TSH which stimulates thyroid glands
T3 and T4 inhibit pituitary release of TSH
thyroid glands
releases T3 and T4
abnormality at the level of the hypothalamus causes excess release of **TRH**
tertiary hyperthyroidism (rare)
⇧ in TRH ripples down hormonal axis
⇧ in TSH
⇧ **in T3 and T4**
normally ⇧ in T3 and T4 shuts down TRH production
but dysfunctional hypothalamus ignores negative feedback
continued ⇧ in TRH
abnormality at the level of the anterior pituitary causes excess release of **TSH**
secondary hyperthyroidism:
• pituitary adenoma
⇧ in TSH ripples down hormonal axis
⇧ TSH
⇧ **in T3 and T4**
normally ⇧ in T3 and T4 shuts down TSH and TRH production
but dysfunctional anterior pituitary ignores negative feedback
continued increase in TSH
abnormality at the level of the thyroid causes excess production of **T3** and **T4**
primary hyperthyroidism:
• Grave's disease
other causes:
• toxic adenoma
• toxic multinodular goiter
autoimmune type 2 hypersensitivity reaction (see map)
production of antibodies to TSH receptor on thyroid
binds and **overstimulates** TSH receptor
⇧ **in T3 and T4**
blocks TSH from binding its receptor
TSH accumulates and signals anterior pituitary to reduce production of TSH via negative feedback
⇩ **TSH**
excessive release of preformed thyroid hormone
• De Quervain's thyroiditis
• struma ovarii
• thyroiditis (granulomatous and lymphocytic)
• factitious thyrotoxicosis
causes clinical manifestations of **thyrotoxicosis**
increased metabolic rate leads to:
• increased bone turnover and osteoporosis (see map)
• increased protein catabolism causing weight loss, myopathy, proximal muscle weakness, and increased appetite
• increased body temperature causing diaphoresis and vasodilation
• increased cardiac beta receptors causing increased heart rate, cardiac output and risk of high output failure and atrial fibrillation
if uncontrolled or untreated
thyroid storm = medical emergency indicated by:
• tachycardia
• fever
• diarrhea
• nausea
• agitation
• delirium
localized deposition of glycosaminoglycans leads to:
• **exopthalmos**
• **pretibial myxedema** (non-pitting)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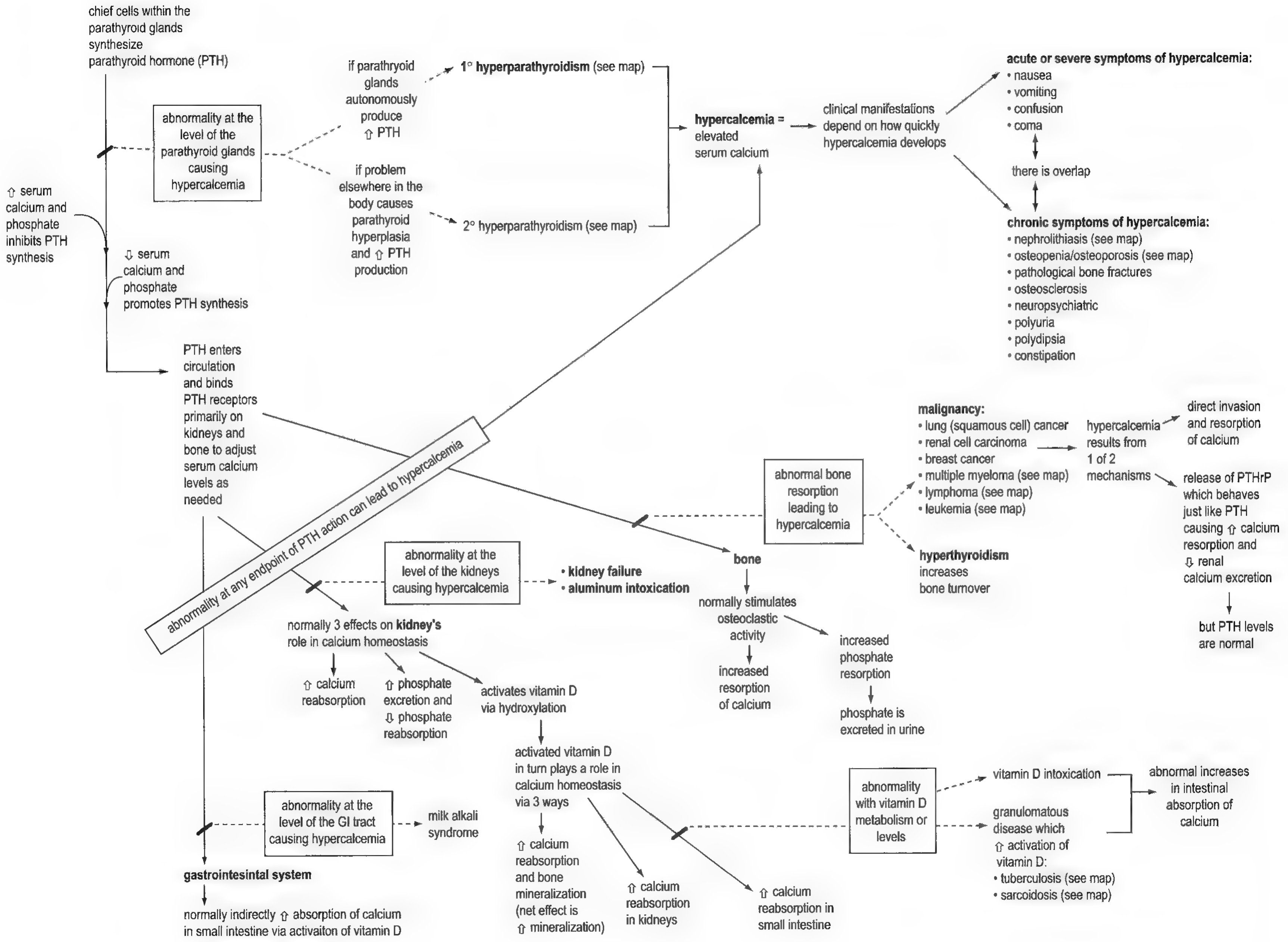
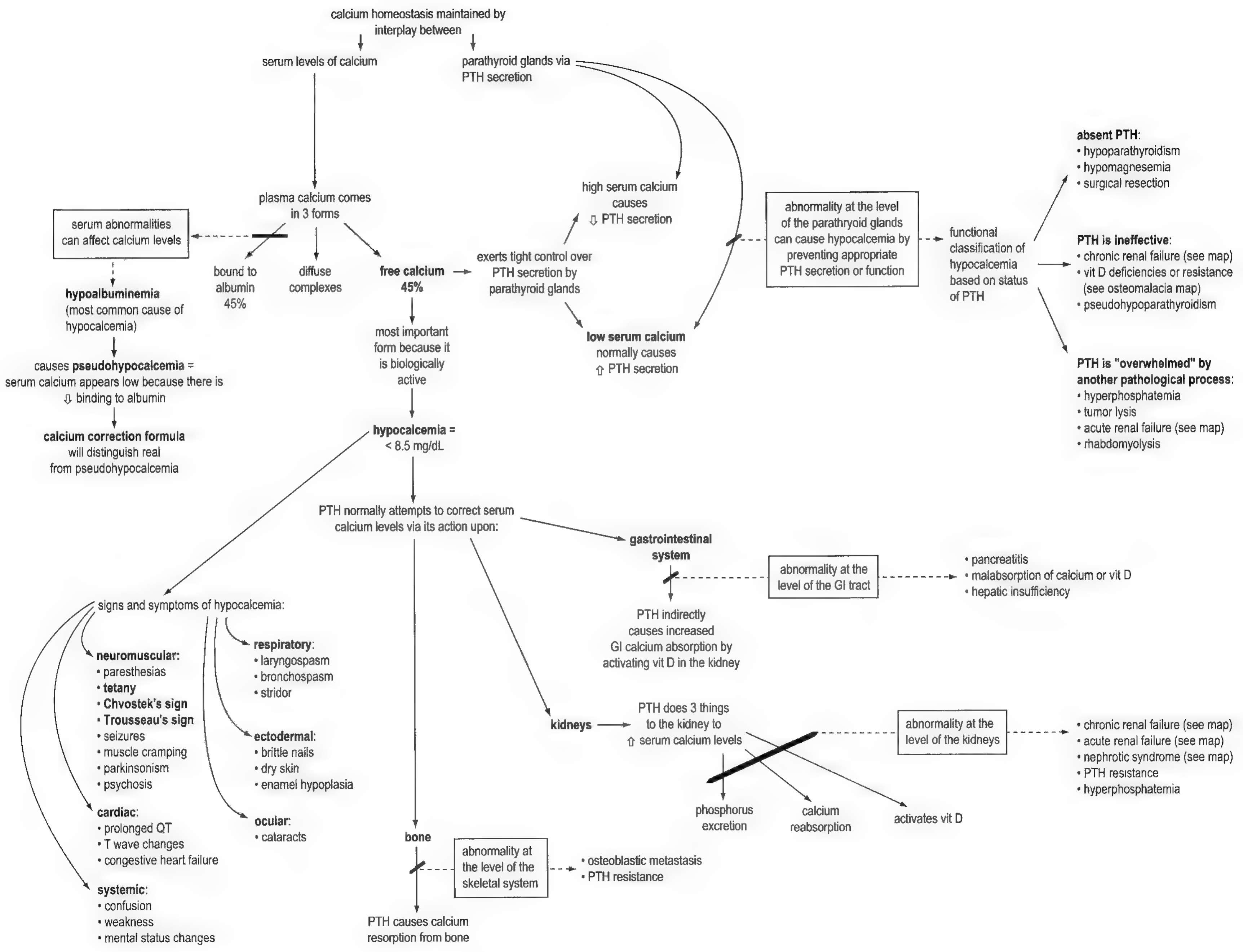
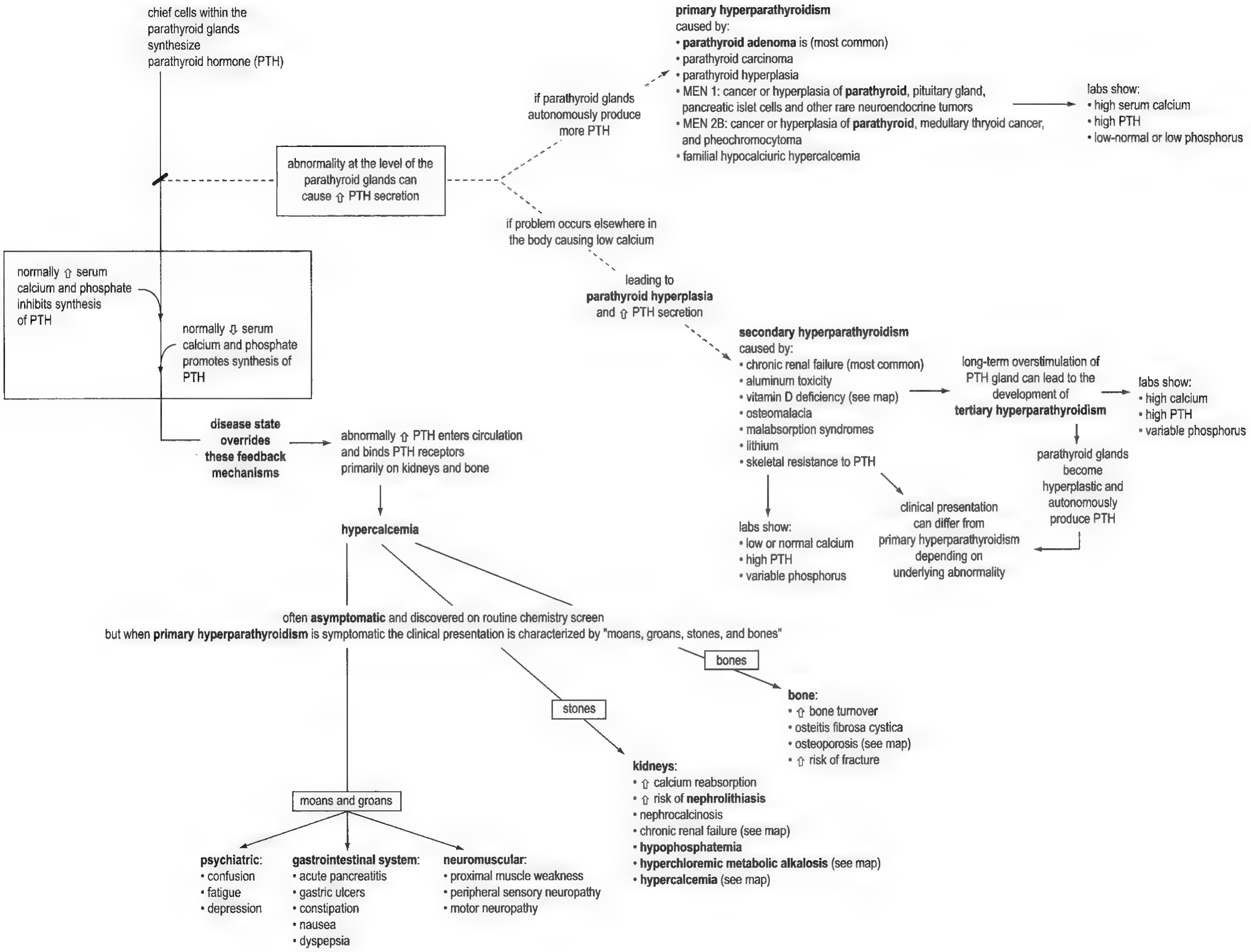
releases TRH which stimulates anterior pituitary
T3 and T4 inhibit hypothalamic release of TRH
anterior pituitary
releases TSH which stimulates thyroid glands
T3 and T4 inhibit pituitary release of TSH
thyroid glands
releases T3 and T4
abnormality at the level of the hypothalamus causes ⇩ release of TRH
tertiary hypothyroidism due to:
• trauma
• tumor
⇩ in TRH ripples down hormonal axis
⇩ in TSH
less T4
abnormality at the level of the anterior pituitary causes ⇩ release of TSH
secondary hypothyroidism due to:
• Sheehan's syndrome
• pituitary tumor
• hypopituitarism
⇩ in TSH ripples down hormonal axis
⇩ T4
abnormality at the level of the thyroid causes decreased release of T3 and T4
primary hypothyroidism due to:
• Hashimoto's thyroiditis (most common)
other causes:
• drugs (including lithium and amiodarone)
• iodine deficiency
• post-ablative
autoimmune process = both B and (primarily) T cells attack thyroid
chronic lymphocytic infiltrate initially causes thyroid to become enlarged and rubbery
but eventually causes gland to become small and fibrotic = atrophic thyroiditis
leads to apoptotic destruction of thyroid cells
thyroid can no longer bind iodide
slow onset as follicular cells are destroyed = subclinical hypothyroidism
clinical symptoms do not appear until 90% of follicular cells destroyed
as T4 slowly decreases TSH increases
⇩ T4 causes clinical manifestations of hypothyroidism
clinical (overt) hypothyroidism
if untreated or severe
myxedema coma:
• hypothermia
• decreased respiratory rate
• coma
• dementia
• psychosis
signs secondary to accumulation of polysaccharides in tissue:
• periorbital edema
• pericardial effusions
• ascites
• myxedema (non-pitting edema)
• hoarseness
• cardiomyopathy
• neuropathy
signs secondary to ⇩ metabolic rate:
• constipation
• fatigue
• weight gain
• cold intolerance
• hair loss
• hung up reflexes
• ⇩ heart rate
• ⇩ cardiac output
signs due to ⇩ in T4:
⇩ LDL receptors = hyperlipidemia
⇩ B12 = macrocytic anemia
⇩ erythropoiesis = normocytic anemia
⇧ prolactin:
• galactorrhea
• infertility
• menstrual irregularities


chief cells within the parathyroid glands synthesize parathyroid hormone (PTH)
⇧ serum calcium and phosphate inhibits PTH synthesis
⇩ serum calcium and phosphate promotes PTH synthesis
abnormality at the level of the parathyroid glands causing hypercalcemia
if parathyroid glands autonomously produce ⇧ PTH
if problem elsewhere in the body causes parathyroid hyperplasia and ⇧ PTH production
1° hyperparathyroidism (see map)
2° hyperparathyroidism (see map)
hypercalcemia = elevated serum calcium
clinical manifestations depend on how quickly hypercalcemia develops
acute or severe symptoms of hypercalcemia:
• nausea
• vomiting
• confusion
• coma
there is overlap
chronic symptoms of hypercalcemia:
• nephrolithiasis (see map)
• osteopenia/osteoporosis (see map)
• pathological bone fractures
• osteosclerosis
• neuropsychiatric
• polyuria
• polydipsia
• constipation
PTH enters circulation and binds PTH receptors primarily on kidneys and bone to adjust serum calcium levels as needed
abnormality at any endpoint of PTH action can lead to hypercalcemia
abnormal bone resorption leading to hypercalcemia
malignancy:
• lung (squamous cell) cancer
• renal cell carcinoma
• breast cancer
• multiple myeloma (see map)
• lymphoma (see map)
• leukemia (see map)
hypercalcemia results from 1 of 2 mechanisms
direct invasion and resorption of calcium
release of PTHrP which behaves just like PTH causing ⇧ calcium resorption and ⇩ renal calcium excretion
but PTH levels are normal
hyperthyroidism increases bone turnover
bone
normally stimulates osteoclastic activity
increased resorption of calcium
increased phosphate resorption
phosphate is excreted in urine
abnormality at the level of the kidneys causing hypercalcemia
• **kidney failure**
• **aluminum intoxication**
normally 3 effects on **kidney's** role in calcium homeostasis
⇧ calcium reabsorption
⇧ phosphate excretion and ⇩ phosphate reabsorption
activates vitamin D via hydroxylation
activated vitamin D in turn plays a role in calcium homeostasis via 3 ways
⇧ calcium reabsorption and bone mineralization (net effect is ⇧ mineralization)
⇧ calcium reabsorption in kidneys
⇧ calcium reabsorption in small intestine
abnormality with vitamin D metabolism or levels
vitamin D intoxication
granulomatous disease which ⇧ activation of vitamin D:
• tuberculosis (see map)
• sarcoidosis (see map)
abnormal increases in intestinal absorption of calcium
abnormality at the level of the GI tract causing hypercalcemia
milk alkali syndrome
gastrointesintal system
normally indirectly ⇧ absorption of calcium in small intestine via activaiton of vitamin D


calcium homeostasis maintained by interplay between
serum levels of calcium
parathyroid glands via PTH secretion
plasma calcium comes in 3 forms
serum abnormalities can affect calcium levels
bound to albumin 45%
diffuse complexes
free calcium 45%
exerts tight control over PTH secretion by parathyroid glands
high serum calcium causes ⇩ PTH secretion
low serum calcium normally causes ⇧ PTH secretion
abnormality at the level of the parathyroid glands can cause hypocalcemia by preventing appropriate PTH secretion or function
functional classification of hypocalcemia based on status of PTH
absent PTH:
• hypoparathyroidism
• hypomagnesemia
• surgical resection
PTH is ineffective:
• chronic renal failure (see map)
• vit D deficiencies or resistance (see osteomalacia map)
• pseudohypoparathyroidism
PTH is "overwhelmed" by another pathological process:
• hyperphosphatemia
• tumor lysis
• acute renal failure (see map)
• rhabdomyolysis
hypoalbuminemia (most common cause of hypocalcemia)
causes **pseudohypocalcemia** = serum calcium appears low because there is ⇩ binding to albumin
calcium correction formula will distinguish real from pseudohypocalcemia
most important form because it is biologically active
hypocalcemia = < 8.5 mg/dL
PTH normally attempts to correct serum calcium levels via its action upon:
gastrointestinal system
abnormality at the level of the GI tract
• pancreatitis
• malabsorption of calcium or vit D
• hepatic insufficiency
PTH indirectly causes increased GI calcium absorption by activating vit D in the kidney
kidneys
PTH does 3 things to the kidney to ⇧ serum calcium levels
abnormality at the level of the kidneys
• chronic renal failure (see map)
• acute renal failure (see map)
• nephrotic syndrome (see map)
• PTH resistance
• hyperphosphatemia
phosphorus excretion
calcium reabsorption
activates vit D
bone
abnormality at the level of the skeletal system
• osteoblastic metastasis
• PTH resistance
PTH causes calcium resorption from bone
signs and symptoms of hypocalcemia:
neuromuscular:
• paresthesias
• **tetany**
• **Chvostek's sign**
• **Trousseau's sign**
• seizures
• muscle cramping
• parkinsonism
• psychosis
cardiac:
• prolonged QT
• T wave changes
• congestive heart failure
systemic:
• confusion
• weakness
• mental status changes
respiratory:
• laryngospasm
• bronchospasm
• stridor
ectodermal:
• brittle nails
• dry skin
• enamel hypoplasia
ocular:
• cataracts



chief cells within the parathyroid glands synthesize parathyroid hormone (PTH)

normally ⇧ serum calcium and phosphate inhibits synthesis of PTH

normally ⇩ serum calcium and phosphate promotes synthesis of PTH

disease state overrides these feedback mechanisms

abnormally ⇧ PTH enters circulation and binds PTH receptors primarily on kidneys and bone

hypercalcemia

abnormality at the level of the parathyroid glands can cause ⇧ PTH secretion

if parathyroid glands autonomously produce more PTH

primary hyperparathyroidism
caused by:
- **parathyroid adenoma** is (most common)
- parathyroid carcinoma
- parathyroid hyperplasia
- MEN 1: cancer or hyperplasia of **parathyroid**, pituitary gland, pancreatic islet cells and other rare neuroendocrine tumors
- MEN 2B: cancer or hyperplasia of **parathyroid**, medullary thryoid cancer, and pheochromocytoma
- familial hypocalciuric hypercalcemia

labs show:
- high serum calcium
- high PTH
- low-normal or low phosphorus

if problem occurs elsewhere in the body causing low calcium

leading to **parathyroid hyperplasia** and ⇧ PTH secretion

secondary hyperparathyroidism
caused by:
- chronic renal failure (most common)
- aluminum toxicity
- vitamin D deficiency (see map)
- osteomalacia
- malabsorption syndromes
- lithium
- skeletal resistance to PTH

labs show:
- low or normal calcium
- high PTH
- variable phosphorus

clinical presentation can differ from primary hyperparathyroidism depending on underlying abnormality

long-term overstimulation of PTH gland can lead to the development of **tertiary hyperparathyroidism**

labs show:
- high calcium
- high PTH
- variable phosphorus

parathyroid glands become hyperplastic and autonomously produce PTH

often **asymptomatic** and discovered on routine chemistry screen
but when **primary hyperparathyroidism** is symptomatic the clinical presentation is characterized by "moans, groans, stones, and bones"

bones

bone:
- ⇧ bone turnover
- osteitis fibrosa cystica
- osteoporosis (see map)
- ⇧ risk of fracture

stones

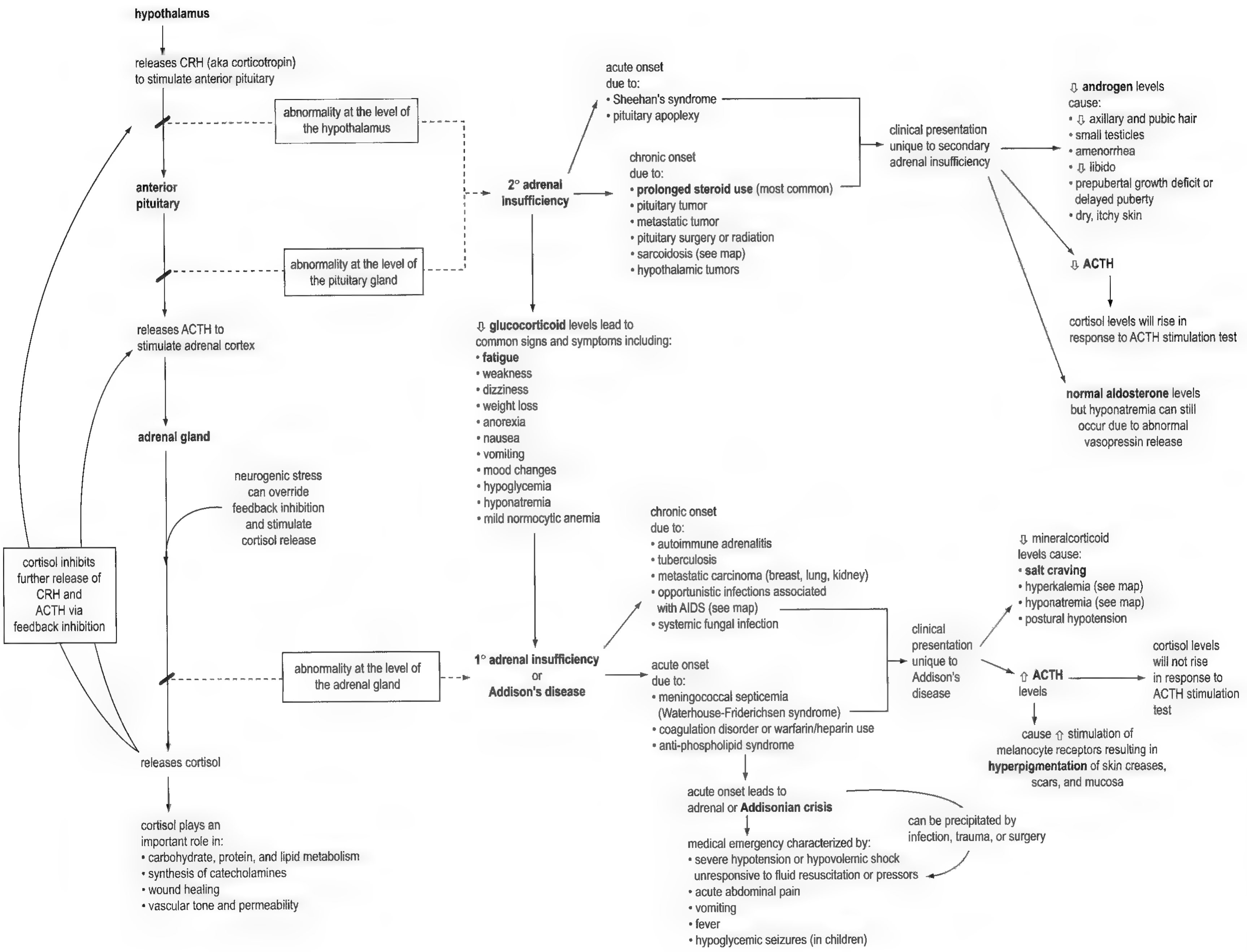
kidneys:
- ⇧ calcium reabsorption
- ⇧ risk of **nephrolithiasis**
- nephrocalcinosis
- chronic renal failure (see map)
- **hypophosphatemia**
- **hyperchloremic metabolic alkalosis** (see map)
- **hypercalcemia** (see map)

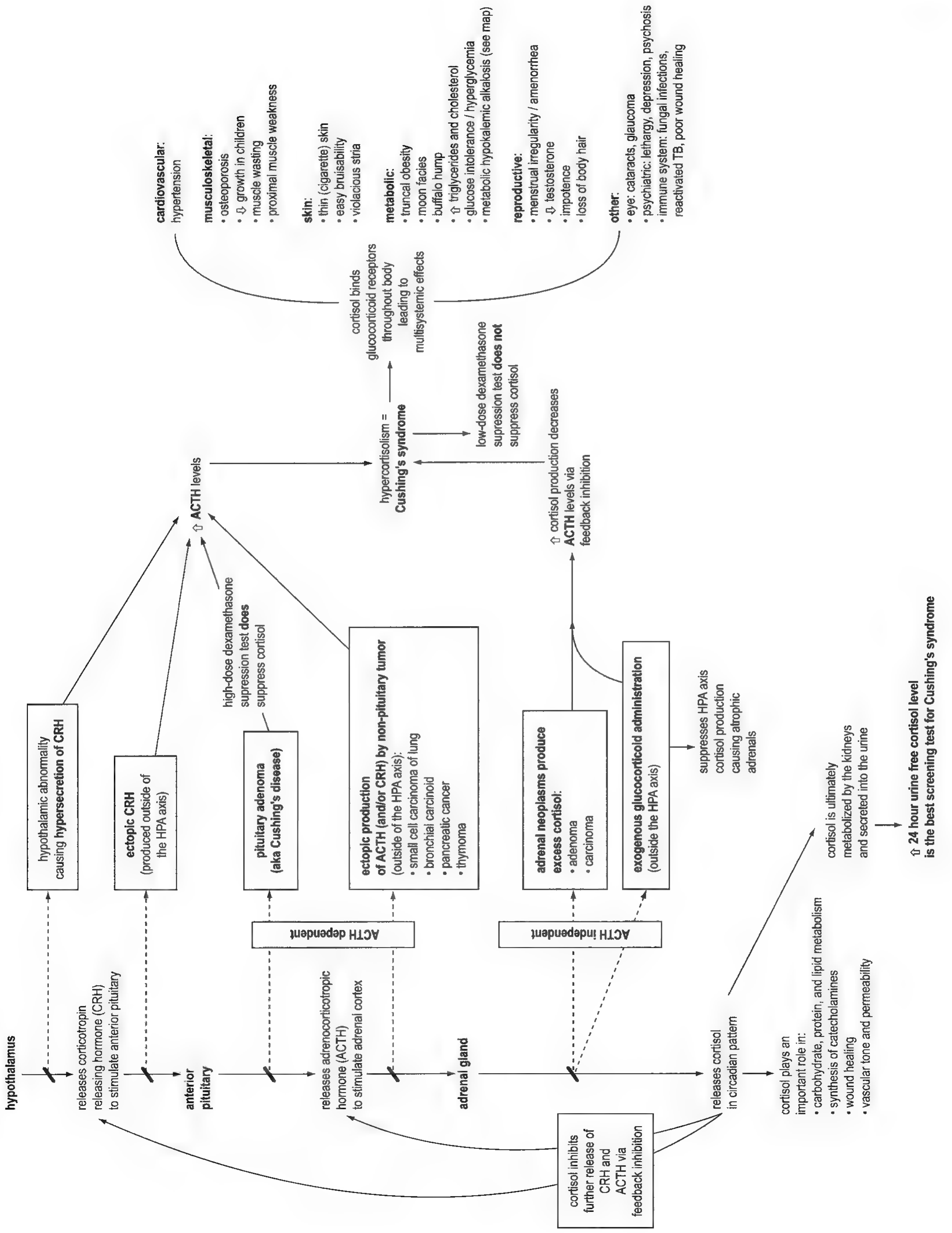
moans and groans

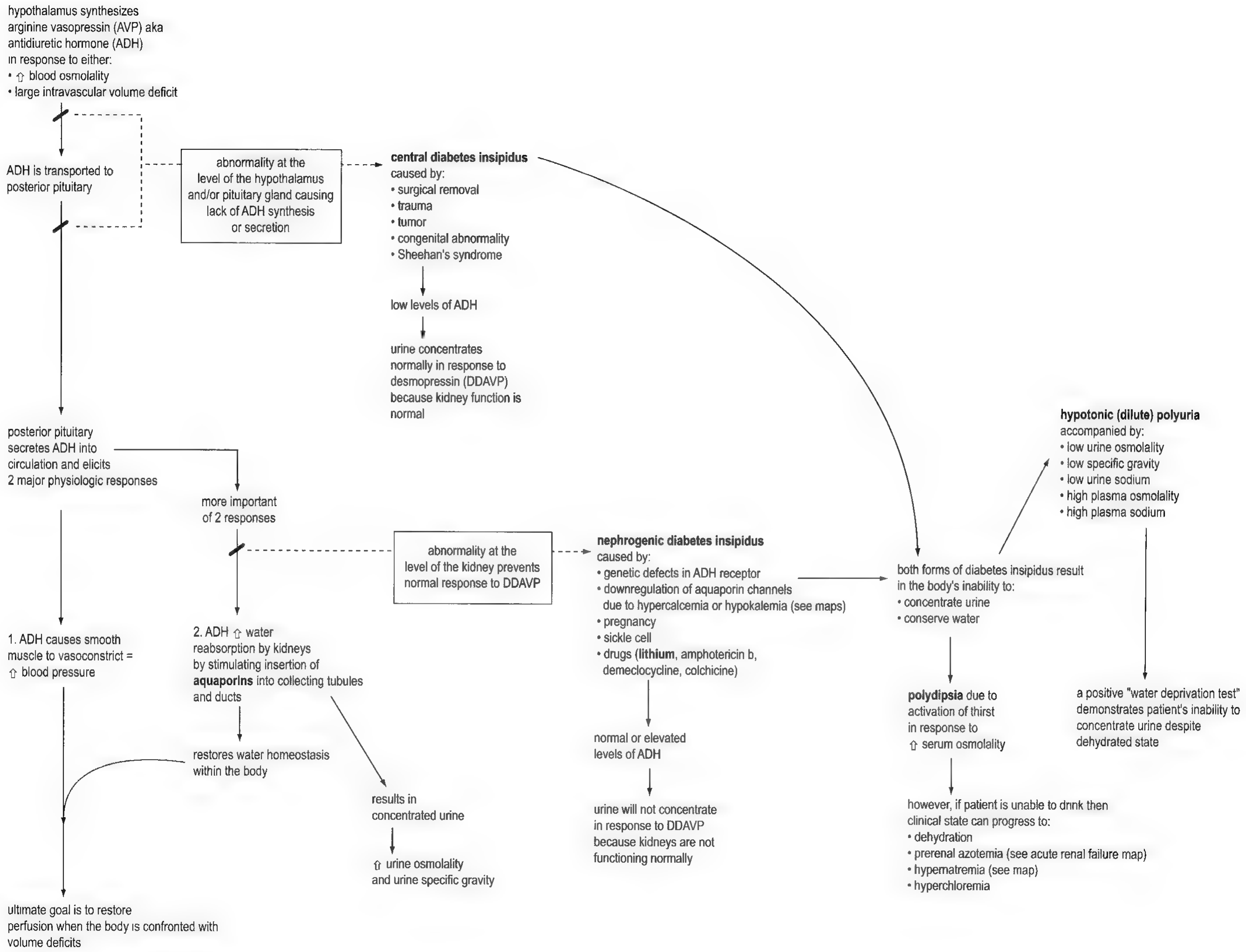
psychiatric:
- confusion
- fatigue
- depression

gastrointestinal system:
- acute pancreatitis
- gastric ulcers
- constipation
- nausea
- dyspepsia

neuromuscular:
- proximal muscle weakness
- peripheral sensory neuropathy
- motor neuropathy


hypothalamus
releases CRH (aka corticotropin) to stimulate anterior pituitary
abnormality at the level of the hypothalamus
anterior pituitary
abnormality at the level of the pituitary gland
releases ACTH to stimulate adrenal cortex
adrenal gland
neurogenic stress can override feedback inhibition and stimulate cortisol release
cortisol inhibits further release of CRH and ACTH via feedback inhibition
abnormality at the level of the adrenal gland
releases cortisol
cortisol plays an important role in:
• carbohydrate, protein, and lipid metabolism
• synthesis of catecholamines
• wound healing
• vascular tone and permeability
2° adrenal insufficiency
acute onset due to:
• Sheehan's syndrome
• pituitary apoplexy
chronic onset due to:
• prolonged steroid use (most common)
• pituitary tumor
• metastatic tumor
• pituitary surgery or radiation
• sarcoidosis (see map)
• hypothalamic tumors
clinical presentation unique to secondary adrenal insufficiency
⇩ androgen levels cause:
• ⇩ axillary and pubic hair
• small testicles
• amenorrhea
• ⇩ libido
• prepubertal growth deficit or delayed puberty
• dry, itchy skin
⇩ ACTH
cortisol levels will rise in response to ACTH stimulation test
normal aldosterone levels but hyponatremia can still occur due to abnormal vasopressin release
⇩ glucocorticoid levels lead to common signs and symptoms including:
• fatigue
• weakness
• dizziness
• weight loss
• anorexia
• nausea
• vomiting
• mood changes
• hypoglycemia
• hyponatremia
• mild normocytic anemia
1° adrenal insufficiency or Addison's disease
chronic onset due to:
• autoimmune adrenalitis
• tuberculosis
• metastatic carcinoma (breast, lung, kidney)
• opportunistic infections associated with AIDS (see map)
• systemic fungal infection
acute onset due to:
• meningococcal septicemia (Waterhouse-Friderichsen syndrome)
• coagulation disorder or warfarin/heparin use
• anti-phospholipid syndrome
clinical presentation unique to Addison's disease
⇩ mineralcorticoid levels cause:
• salt craving
• hyperkalemia (see map)
• hyponatremia (see map)
• postural hypotension
⇧ ACTH levels
cortisol levels will not rise in response to ACTH stimulation test
cause ⇧ stimulation of melanocyte receptors resulting in hyperpigmentation of skin creases, scars, and mucosa
acute onset leads to adrenal or Addisonian crisis
can be precipitated by infection, trauma, or surgery
medical emergency characterized by:
• severe hypotension or hypovolemic shock unresponsive to fluid resuscitation or pressors
• acute abdominal pain
• vomiting
• fever
• hypoglycemic seizures (in children)


hypothalamus
releases corticotropin releasing hormone (CRH) to stimulate anterior pituitary
anterior pituitary
releases adrenocorticotropic hormone (ACTH) to stimulate adrenal cortex
adrenal gland
releases cortisol in circadian pattern
cortisol plays an important role in:
• carbohydrate, protein, and lipid metabolism
• synthesis of catecholamines
• wound healing
• vascular tone and permeability
cortisol inhibits further release of CRH and ACTH via feedback inhibition
cortisol is ultimately metabolized by the kidneys and secreted into the urine
⇧ 24 hour urine free cortisol level is the best screening test for Cushing's syndrome
ACTH dependent
ACTH independent
hypothalamic abnormality causing hypersecretion of CRH
ectopic CRH (produced outside of the HPA axis)
pituitary adenoma (aka Cushing's disease)
high-dose dexamethasone supression test does suppress cortisol
ectopic production of ACTH (and/or CRH) by non-pituitary tumor (outside of the HPA axis):
• small cell carcinoma of lung
• bronchial carcinoid
• pancreatic cancer
• thymoma
⇧ ACTH levels
adrenal neoplasms produce excess cortisol:
• adenoma
• carcinoma
exogenous glucocorticoid administration (outside the HPA axis)
suppresses HPA axis cortisol production causing atrophic adrenals
⇧ cortisol production decreases ACTH levels via feedback inhibition
hypercortisolism = Cushing's syndrome
low-dose dexamethasone supression test does not suppress cortisol
cortisol binds glucocorticoid receptors throughout body leading to multisystemic effects
cardiovascular:
hypertension
musculoskeletal:
• osteoporosis
• ⇩ growth in children
• muscle wasting
• proximal muscle weakness
skin:
• thin (cigarette) skin
• easy bruisability
• violacious stria
metabolic:
• truncal obesity
• moon facies
• buffalo hump
• ⇧ triglycerides and cholesterol
• glucose intolerance / hyperglycemia
• metabolic hypokalemic alkalosis (see map)
reproductive:
• menstrual irregularity / amenorrhea
• ⇩ testosterone
• impotence
• loss of body hair
other:
• eye: cataracts, glaucoma
• psychiatric: lethargy, depression, psychosis
• immune system: fungal infections, reactivated TB, poor wound healing



hypothalamus synthesizes arginine vasopressin (AVP) aka antidiuretic hormone (ADH) in response to either:
- ⇧ blood osmolality
- large intravascular volume deficit

ADH is transported to posterior pituitary

abnormality at the level of the hypothalamus and/or pituitary gland causing lack of ADH synthesis or secretion

central diabetes insipidus
caused by:
- surgical removal
- trauma
- tumor
- congenital abnormality
- Sheehan's syndrome

low levels of ADH

urine concentrates normally in response to desmopressin (DDAVP) because kidney function is normal

posterior pituitary secretes ADH into circulation and elicits 2 major physiologic responses

more important of 2 responses

abnormality at the level of the kidney prevents normal response to DDAVP

nephrogenic diabetes insipidus
caused by:
- genetic defects in ADH receptor
- downregulation of aquaporin channels due to hypercalcemia or hypokalemia (see maps)
- pregnancy
- sickle cell
- drugs (**lithium**, amphotericin b, demeclocycline, colchicine)

normal or elevated levels of ADH

urine will not concentrate in response to DDAVP because kidneys are not functioning normally

both forms of diabetes insipidus result in the body's inability to:
- concentrate urine
- conserve water

hypotonic (dilute) polyuria
accompanied by:
- low urine osmolality
- low specific gravity
- low urine sodium
- high plasma osmolality
- high plasma sodium

a positive "water deprivation test" demonstrates patient's inability to concentrate urine despite dehydrated state

polydipsia due to activation of thirst in response to ⇧ serum osmolality

however, if patient is unable to drink then clinical state can progress to:
- dehydration
- prerenal azotemia (see acute renal failure map)
- hypernatremia (see map)
- hyperchloremia

1. ADH causes smooth muscle to vasoconstrict = ⇧ blood pressure

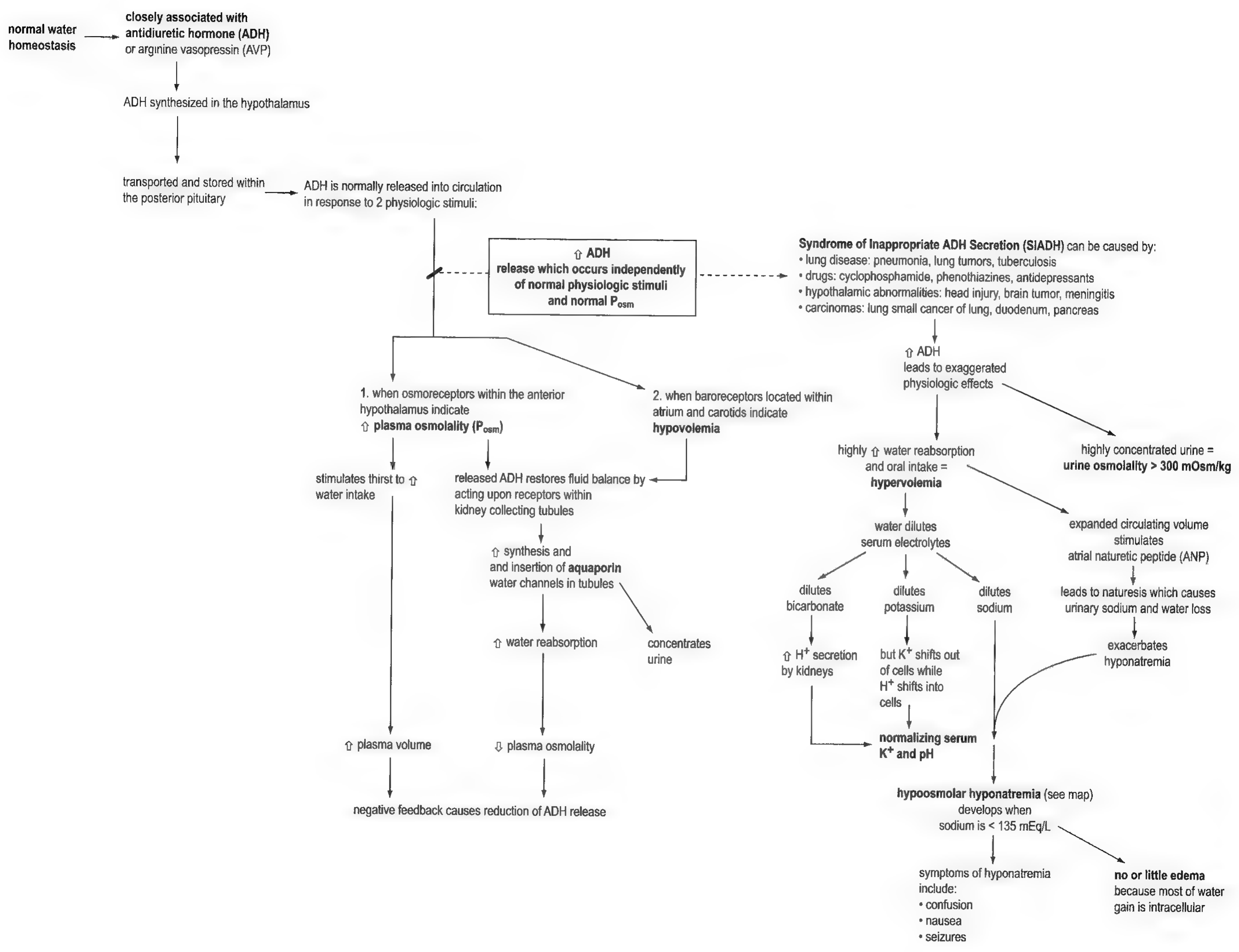
2. ADH ⇧ water reabsorption by kidneys by stimulating insertion of **aquaporins** into collecting tubules and ducts

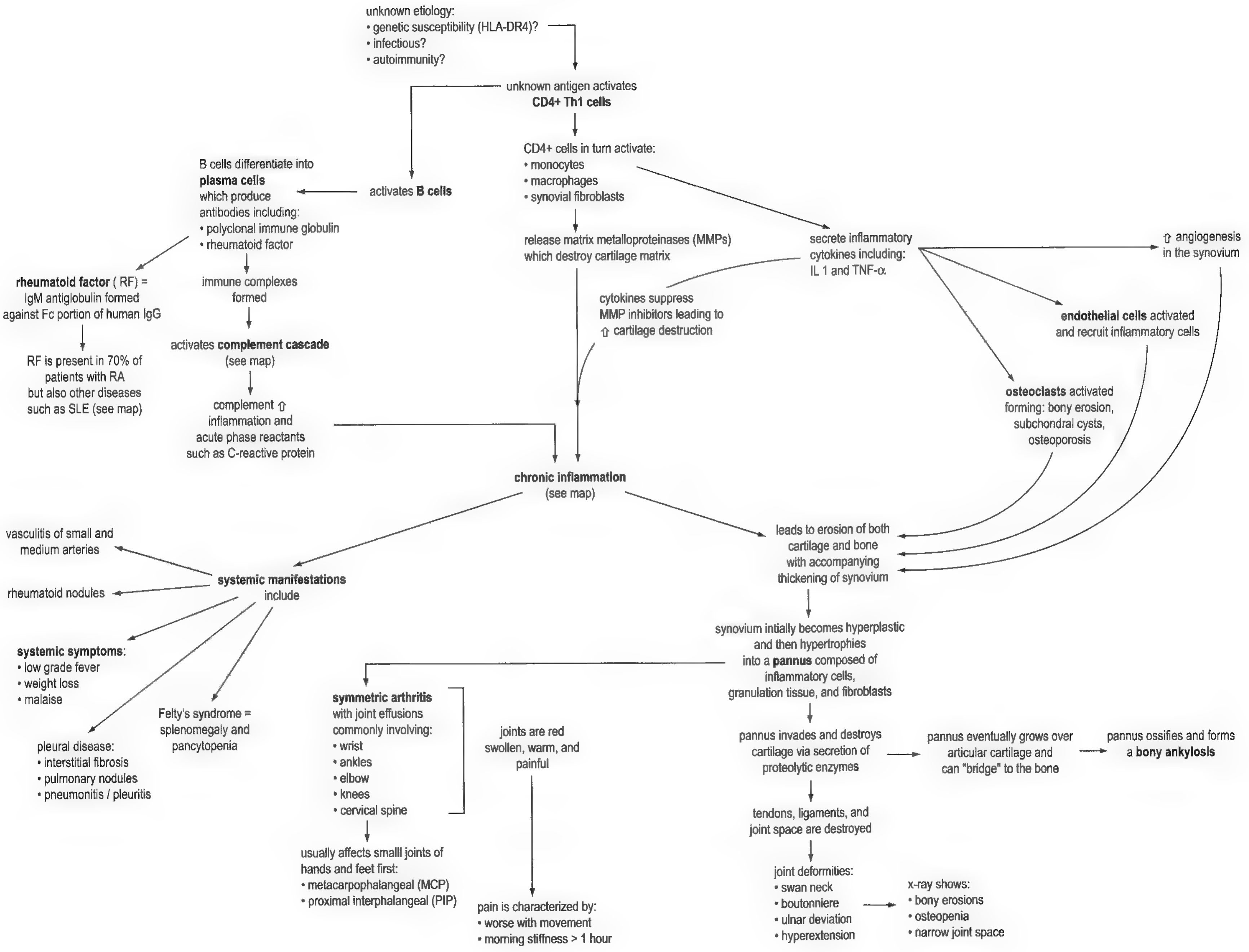
restores water homeostasis within the body

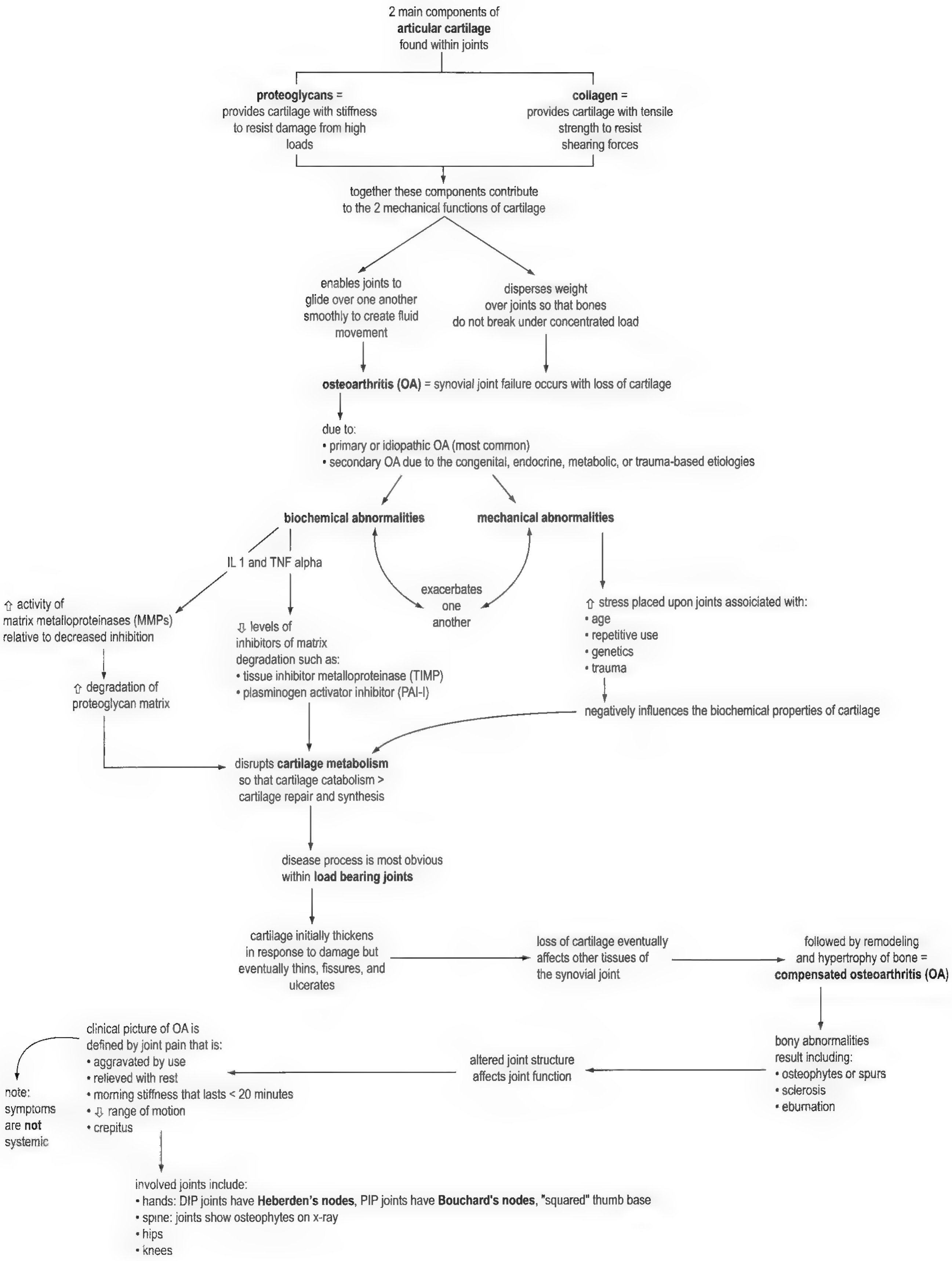
results in concentrated urine

⇧ urine osmolality and urine specific gravity

ultimate goal is to restore perfusion when the body is confronted with volume deficits


normal water homeostasis
closely associated with antidiuretic hormone (ADH) or arginine vasopressin (AVP)
ADH synthesized in the hypothalamus
transported and stored within the posterior pituitary
ADH is normally released into circulation in response to 2 physiologic stimuli:
⇧ ADH release which occurs independently of normal physiologic stimuli and normal P_{osm}
Syndrome of Inappropriate ADH Secretion (SIADH) can be caused by:
• lung disease: pneumonia, lung tumors, tuberculosis
• drugs: cyclophosphamide, phenothiazines, antidepressants
• hypothalamic abnormalities: head injury, brain tumor, meningitis
• carcinomas: lung small cancer of lung, duodenum, pancreas
⇧ ADH leads to exaggerated physiologic effects
1. when osmoreceptors within the anterior hypothalamus indicate ⇧ plasma osmolality (P_{osm})
2. when baroreceptors located within atrium and carotids indicate hypovolemia
stimulates thirst to ⇧ water intake
released ADH restores fluid balance by acting upon receptors within kidney collecting tubules
⇧ synthesis and and insertion of aquaporin water channels in tubules
⇧ water reabsorption
concentrates urine
⇧ plasma volume
⇩ plasma osmolality
negative feedback causes reduction of ADH release
highly ⇧ water reabsorption and oral intake = hypervolemia
highly concentrated urine = urine osmolality > 300 mOsm/kg
water dilutes serum electrolytes
expanded circulating volume stimulates atrial naturetic peptide (ANP)
dilutes bicarbonate
dilutes potassium
dilutes sodium
leads to naturesis which causes urinary sodium and water loss
⇧ H^+ secretion by kidneys
but K^+ shifts out of cells while H^+ shifts into cells
exacerbates hyponatremia
normalizing serum K^+ and pH
hypoosmolar hyponatremia (see map) develops when sodium is < 135 mEq/L
symptoms of hyponatremia include:
• confusion
• nausea
• seizures
no or little edema because most of water gain is intracellular


unknown etiology:
• genetic susceptibility (HLA-DR4)?
• infectious?
• autoimmunity?
unknown antigen activates **CD4+ Th1 cells**
CD4+ cells in turn activate:
• monocytes
• macrophages
• synovial fibroblasts
release matrix metalloproteinases (MMPs) which destroy cartilage matrix
secrete inflammatory cytokines including: IL 1 and TNF-α
⇧ angiogenesis in the synovium
endothelial cells activated and recruit inflammatory cells
osteoclasts activated forming: bony erosion, subchondral cysts, osteoporosis
cytokines suppress MMP inhibitors leading to ⇧ cartilage destruction
activates **B cells**
B cells differentiate into **plasma cells** which produce antibodies including:
• polyclonal immune globulin
• rheumatoid factor
rheumatoid factor (RF) = IgM antiglobulin formed against Fc portion of human IgG
RF is present in 70% of patients with RA but also other diseases such as SLE (see map)
immune complexes formed
activates **complement cascade** (see map)
complement ⇧ inflammation and acute phase reactants such as C-reactive protein
chronic inflammation (see map)
leads to erosion of both cartilage and bone with accompanying thickening of synovium
synovium intially becomes hyperplastic and then hypertrophies into a **pannus** composed of inflammatory cells, granulation tissue, and fibroblasts
pannus invades and destroys cartilage via secretion of proteolytic enzymes
pannus eventually grows over articular cartilage and can "bridge" to the bone
pannus ossifies and forms a **bony ankylosis**
tendons, ligaments, and joint space are destroyed
joint deformities:
• swan neck
• boutonniere
• ulnar deviation
• hyperextension
x-ray shows:
• bony erosions
• osteopenia
• narrow joint space
symmetric arthritis with joint effusions commonly involving:
• wrist
• ankles
• elbow
• knees
• cervical spine
usually affects smalll joints of hands and feet first:
• metacarpophalangeal (MCP)
• proximal interphalangeal (PIP)
joints are red swollen, warm, and painful
pain is characterized by:
• worse with movement
• morning stiffness > 1 hour
systemic manifestations include
vasculitis of small and medium arteries
rheumatoid nodules
systemic symptoms:
• low grade fever
• weight loss
• malaise
pleural disease:
• interstitial fibrosis
• pulmonary nodules
• pneumonitis / pleuritis
Felty's syndrome = splenomegaly and pancytopenia



2 main components of **articular cartilage** found within joints

proteoglycans = provides cartilage with stiffness to resist damage from high loads

collagen = provides cartilage with tensile strength to resist shearing forces

together these components contribute to the 2 mechanical functions of cartilage

enables joints to glide over one another smoothly to create fluid movement

disperses weight over joints so that bones do not break under concentrated load

osteoarthritis (OA) = synovial joint failure occurs with loss of cartilage

due to:
- primary or idiopathic OA (most common)
- secondary OA due to the congenital, endocrine, metabolic, or trauma-based etiologies

biochemical abnormalities

mechanical abnormalities

exacerbates one another

IL 1 and TNF alpha

⇧ activity of matrix metalloproteinases (MMPs) relative to decreased inhibition

⇧ degradation of proteoglycan matrix

⇩ levels of inhibitors of matrix degradation such as:
- tissue inhibitor metalloproteinase (TIMP)
- plasminogen activator inhibitor (PAI-I)

⇧ stress placed upon joints assoiciated with:
- age
- repetitive use
- genetics
- trauma

negatively influences the biochemical properties of cartilage

disrupts **cartilage metabolism** so that cartilage catabolism > cartilage repair and synthesis

disease process is most obvious within **load bearing joints**

cartilage initially thickens in response to damage but eventually thins, fissures, and ulcerates

loss of cartilage eventually affects other tissues of the synovial joint

followed by remodeling and hypertrophy of bone = **compensated osteoarthritis (OA)**

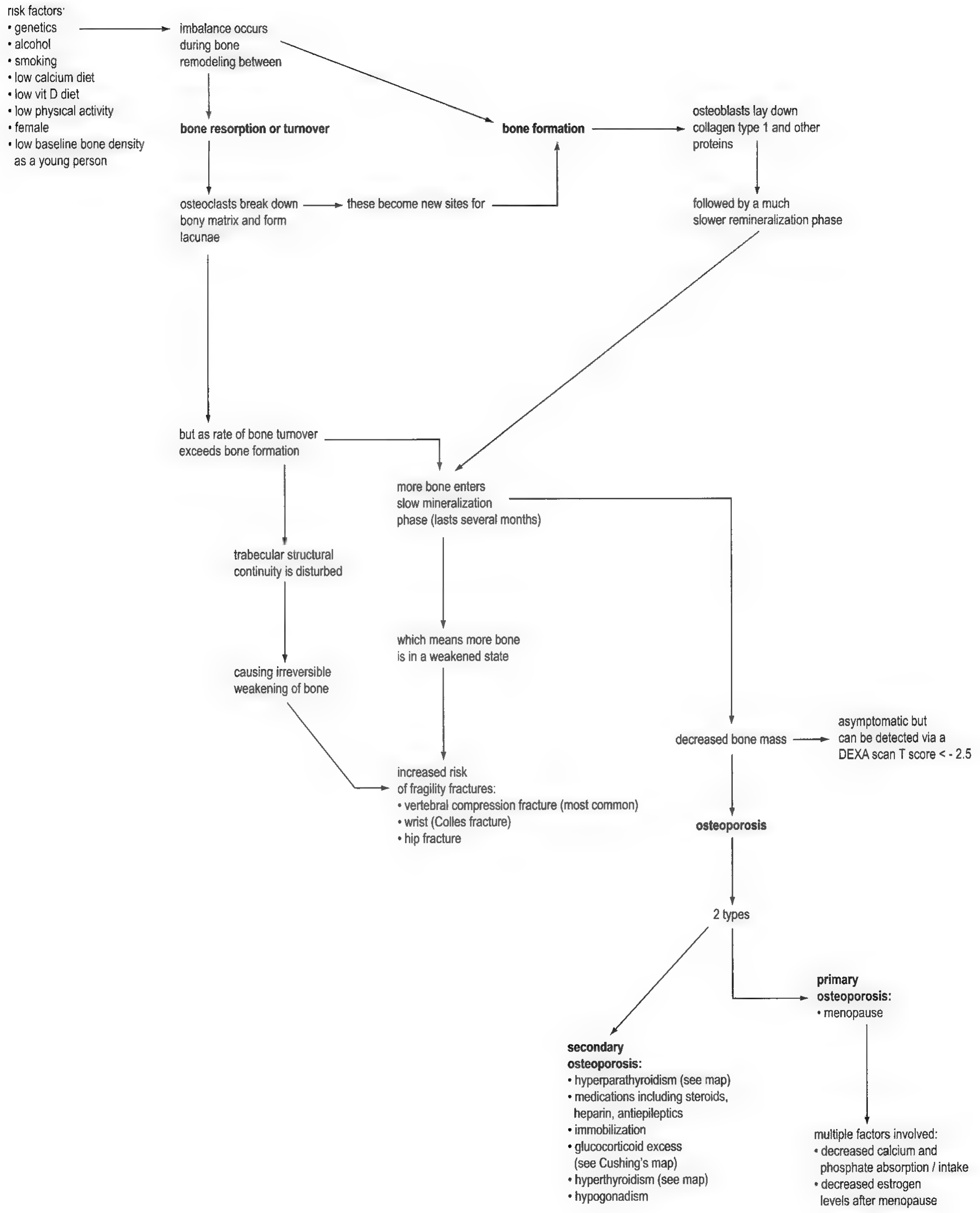
bony abnormalities result including:
- osteophytes or spurs
- sclerosis
- eburnation

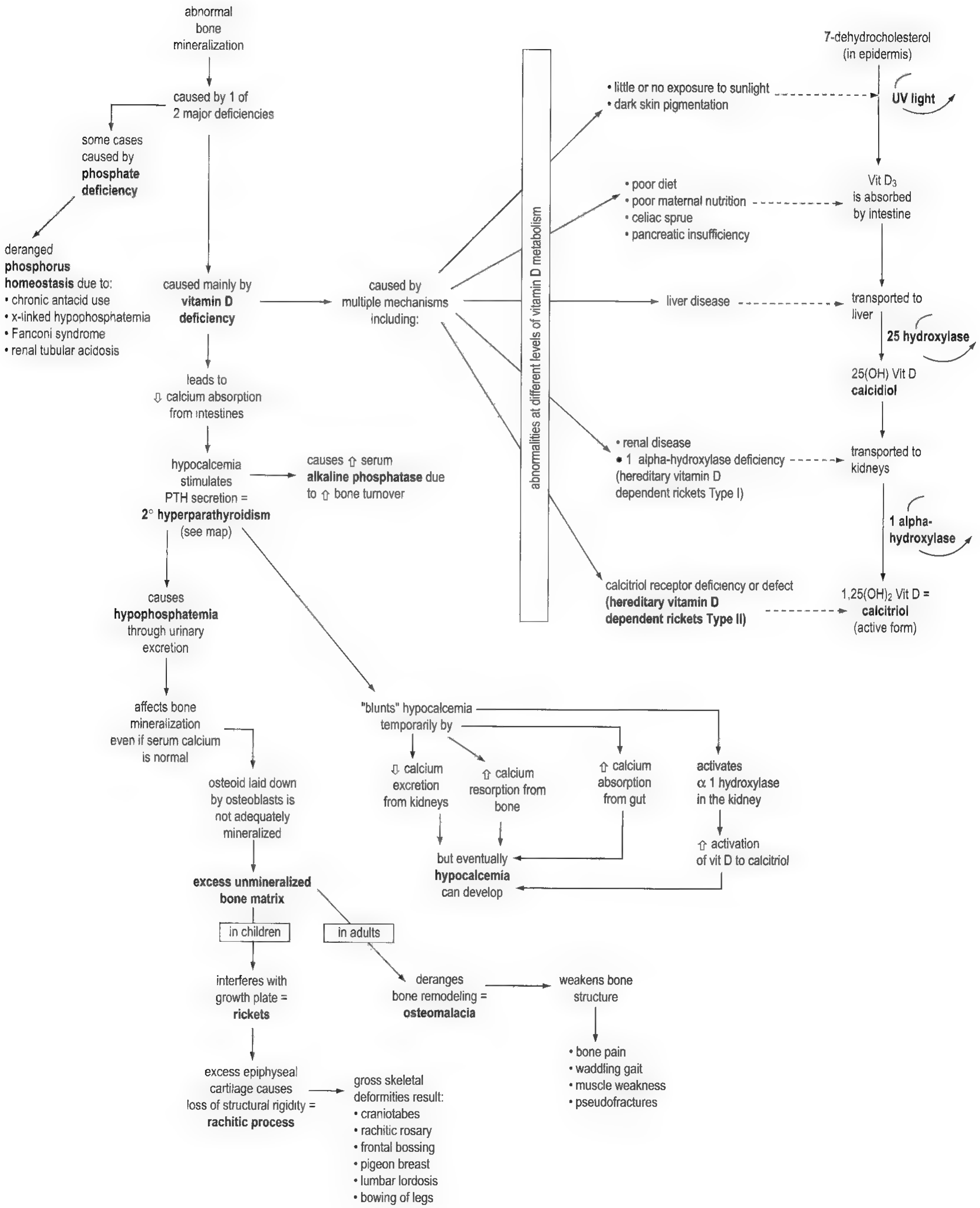
altered joint structure affects joint function

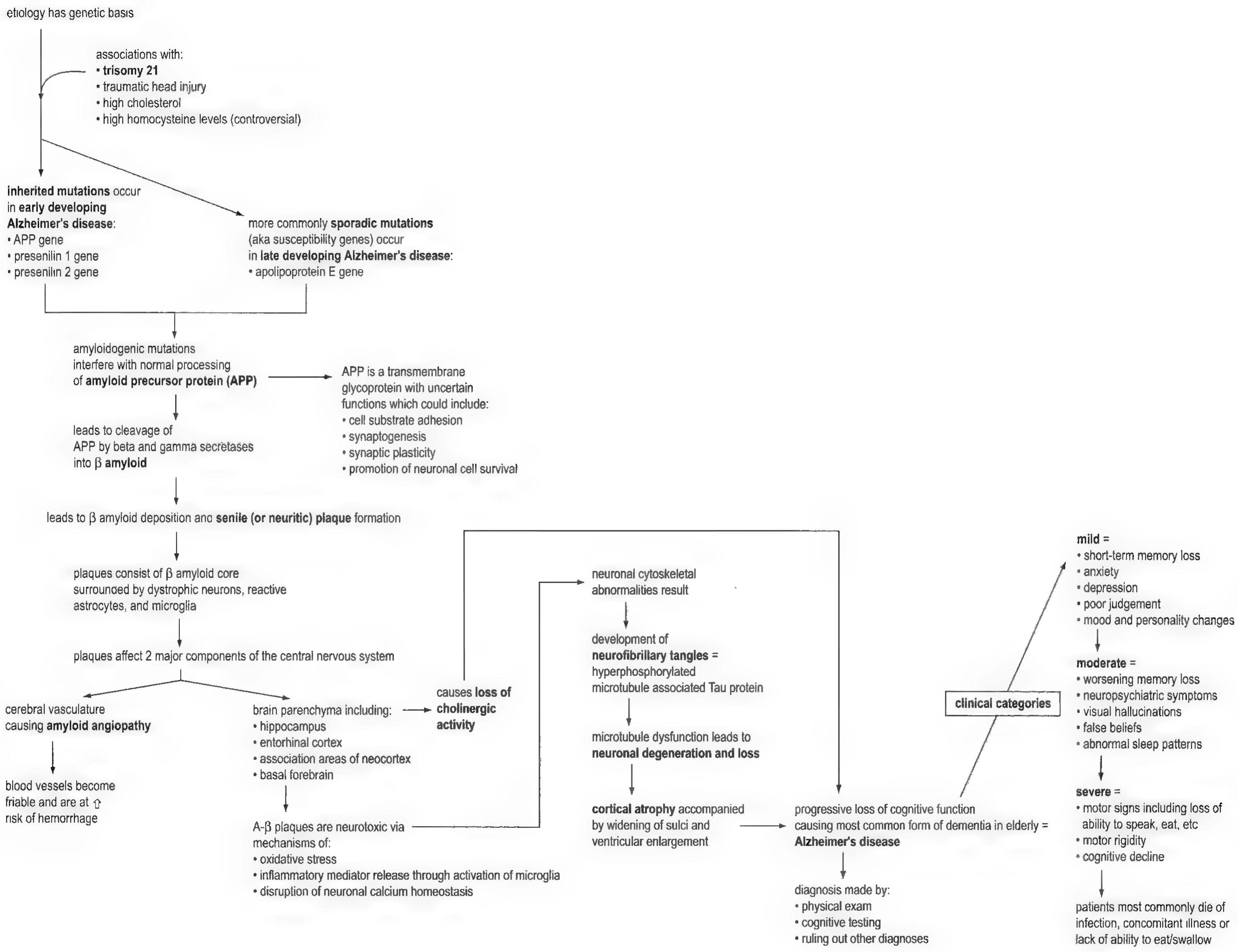
clinical picture of OA is defined by joint pain that is:
- aggravated by use
- relieved with rest
- morning stiffness that lasts < 20 minutes
- ⇩ range of motion
- crepitus

note: symptoms are **not** systemic

involved joints include:
- hands: DIP joints have **Heberden's nodes**, PIP joints have **Bouchard's nodes**, "squared" thumb base
- spine: joints show osteophytes on x-ray
- hips
- knees


risk factors:
• genetics
• alcohol
• smoking
• low calcium diet
• low vit D diet
• low physical activity
• female
• low baseline bone density as a young person
imbalance occurs during bone remodeling between
bone resorption or turnover
bone formation
osteoblasts lay down collagen type 1 and other proteins
osteoclasts break down bony matrix and form lacunae
these become new sites for
followed by a much slower remineralization phase
but as rate of bone turnover exceeds bone formation
more bone enters slow mineralization phase (lasts several months)
trabecular structural continuity is disturbed
which means more bone is in a weakened state
causing irreversible weakening of bone
decreased bone mass
asymptomatic but can be detected via a DEXA scan T score < - 2.5
increased risk of fragility fractures:
• vertebral compression fracture (most common)
• wrist (Colles fracture)
• hip fracture
osteoporosis
2 types
primary osteoporosis:
• menopause
secondary osteoporosis:
• hyperparathyroidism (see map)
• medications including steroids, heparin, antiepileptics
• immobilization
• glucocorticoid excess (see Cushing's map)
• hyperthyroidism (see map)
• hypogonadism
multiple factors involved:
• decreased calcium and phosphate absorption / intake
• decreased estrogen levels after menopause


abnormal bone mineralization
caused by 1 of 2 major deficiencies
some cases caused by **phosphate deficiency**
deranged **phosphorus homeostasis** due to:
• chronic antacid use
• x-linked hypophosphatemia
• Fanconi syndrome
• renal tubular acidosis
caused mainly by **vitamin D deficiency**
caused by multiple mechanisms including:
abnormalities at different levels of vitamin D metabolism
• little or no exposure to sunlight
• dark skin pigmentation
• poor diet
• poor maternal nutrition
• celiac sprue
• pancreatic insufficiency
liver disease
• renal disease
• 1 alpha-hydroxylase deficiency (hereditary vitamin D dependent rickets Type I)
calcitriol receptor deficiency or defect **(hereditary vitamin D dependent rickets Type II)**
7-dehydrocholesterol (in epidermis)
UV light
Vit D_3 is absorbed by intestine
transported to liver
25 hydroxylase
25(OH) Vit D **calcidiol**
transported to kidneys
1 alpha-hydroxylase
$1,25(OH)_2$ Vit D = **calcitriol** (active form)
leads to ⇩ calcium absorption from intestines
hypocalcemia stimulates PTH secretion = **2° hyperparathyroidism** (see map)
causes ⇧ serum **alkaline phosphatase** due to ⇧ bone turnover
causes **hypophosphatemia** through urinary excretion
affects bone mineralization even if serum calcium is normal
osteoid laid down by osteoblasts is not adequately mineralized
excess unmineralized bone matrix
"blunts" hypocalcemia temporarily by
⇩ calcium excretion from kidneys
⇧ calcium resorption from bone
⇧ calcium absorption from gut
activates α 1 hydroxylase in the kidney
⇧ activation of vit D to calcitriol
but eventually **hypocalcemia** can develop
in children
in adults
interferes with growth plate = **rickets**
deranges bone remodeling = **osteomalacia**
weakens bone structure
• bone pain
• waddling gait
• muscle weakness
• pseudofractures
excess epiphyseal cartilage causes loss of structural rigidity = **rachitic process**
gross skeletal deformities result:
• craniotabes
• rachitic rosary
• frontal bossing
• pigeon breast
• lumbar lordosis
• bowing of legs



etiology has genetic basis

associations with:
- **trisomy 21**
- traumatic head injury
- high cholesterol
- high homocysteine levels (controversial)

inherited mutations occur in **early developing Alzheimer's disease**:
- APP gene
- presenilin 1 gene
- presenilin 2 gene

more commonly **sporadic mutations** (aka susceptibility genes) occur in **late developing Alzheimer's disease**:
- apolipoprotein E gene

amyloidogenic mutations interfere with normal processing of **amyloid precursor protein (APP)**

APP is a transmembrane glycoprotein with uncertain functions which could include:
- cell substrate adhesion
- synaptogenesis
- synaptic plasticity
- promotion of neuronal cell survival

leads to cleavage of APP by beta and gamma secretases into β **amyloid**

leads to β amyloid deposition and **senile (or neuritic) plaque** formation

plaques consist of β amyloid core surrounded by dystrophic neurons, reactive astrocytes, and microglia

plaques affect 2 major components of the central nervous system

cerebral vasculature causing **amyloid angiopathy**

blood vessels become friable and are at ⇧ risk of hemorrhage

brain parenchyma including:
- hippocampus
- entorhinal cortex
- association areas of neocortex
- basal forebrain

causes **loss of cholinergic activity**

A-β plaques are neurotoxic via mechanisms of:
- oxidative stress
- inflammatory mediator release through activation of microglia
- disruption of neuronal calcium homeostasis

neuronal cytoskeletal abnormalities result

development of **neurofibrillary tangles** = hyperphosphorylated microtubule associated Tau protein

microtubule dysfunction leads to **neuronal degeneration and loss**

cortical atrophy accompanied by widening of sulci and ventricular enlargement

progressive loss of cognitive function causing most common form of dementia in elderly = **Alzheimer's disease**

diagnosis made by:
- physical exam
- cognitive testing
- ruling out other diagnoses

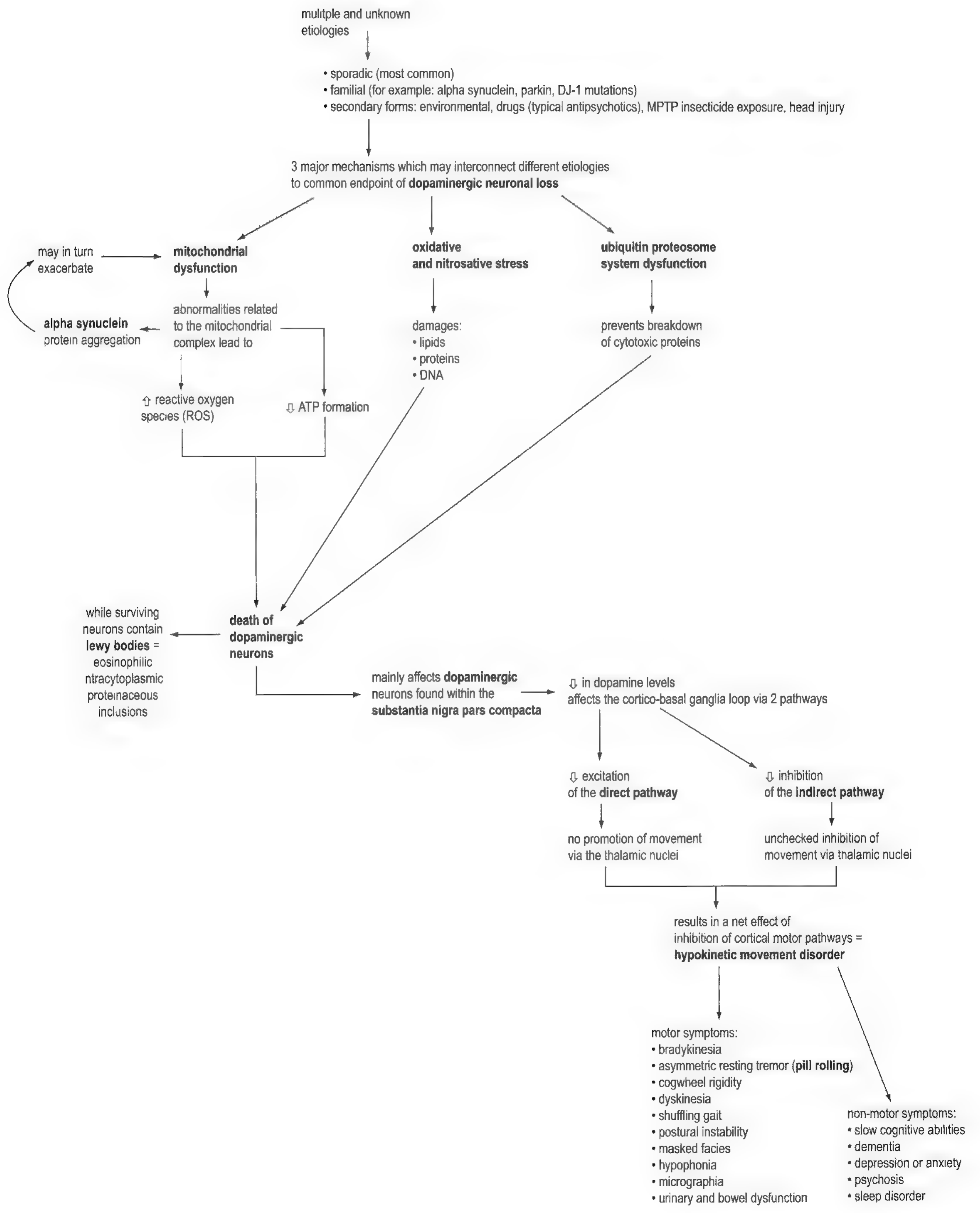
clinical categories

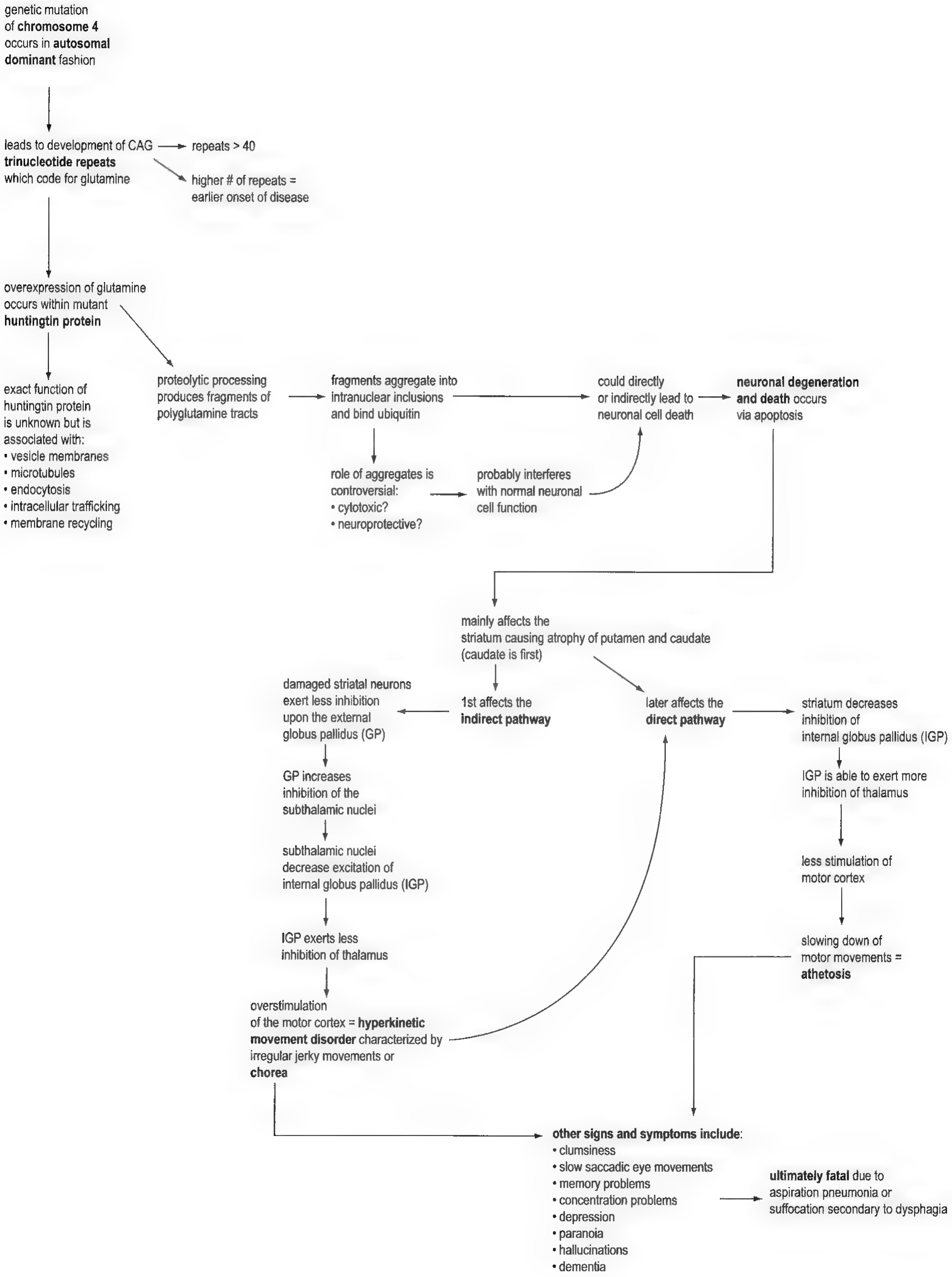
mild =
- short-term memory loss
- anxiety
- depression
- poor judgement
- mood and personality changes

moderate =
- worsening memory loss
- neuropsychiatric symptoms
- visual hallucinations
- false beliefs
- abnormal sleep patterns

severe =
- motor signs including loss of ability to speak, eat, etc
- motor rigidity
- cognitive decline

patients most commonly die of infection, concomitant illness or lack of ability to eat/swallow


mulitple and unknown etiologies
• sporadic (most common)
• familial (for example: alpha synuclein, parkin, DJ-1 mutations)
• secondary forms: environmental, drugs (typical antipsychotics), MPTP insecticide exposure, head injury
3 major mechanisms which may interconnect different etiologies to common endpoint of **dopaminergic neuronal loss**
may in turn exacerbate
mitochondrial dysfunction
oxidative and nitrosative stress
ubiquitin proteosome system dysfunction
alpha synuclein protein aggregation
abnormalities related to the mitochondrial complex lead to
damages:
• lipids
• proteins
• DNA
prevents breakdown of cytotoxic proteins
⇧ reactive oxygen species (ROS)
⇩ ATP formation
while surviving neurons contain **lewy bodies** = eosinophilic intracytoplasmic proteinaceous inclusions
death of dopaminergic neurons
mainly affects **dopaminergic** neurons found within the **substantia nigra pars compacta**
⇩ in dopamine levels affects the cortico-basal ganglia loop via 2 pathways
⇩ excitation of the **direct pathway**
⇩ inhibition of the **indirect pathway**
no promotion of movement via the thalamic nuclei
unchecked inhibition of movement via thalamic nuclei
results in a net effect of inhibition of cortical motor pathways = **hypokinetic movement disorder**
motor symptoms:
• bradykinesia
• asymmetric resting tremor (**pill rolling**)
• cogwheel rigidity
• dyskinesia
• shuffling gait
• postural instability
• masked facies
• hypophonia
• micrographia
• urinary and bowel dysfunction
non-motor symptoms:
• slow cognitive abilities
• dementia
• depression or anxiety
• psychosis
• sleep disorder



genetic mutation of **chromosome 4** occurs in **autosomal dominant** fashion

leads to development of CAG **trinucleotide repeats** which code for glutamine

repeats > 40

higher # of repeats = earlier onset of disease

overexpression of glutamine occurs within mutant **huntingtin protein**

exact function of huntingtin protein is unknown but is associated with:

- vesicle membranes
- microtubules
- endocytosis
- intracellular trafficking
- membrane recycling

proteolytic processing produces fragments of polyglutamine tracts

fragments aggregate into intranuclear inclusions and bind ubiquitin

role of aggregates is controversial:

- cytotoxic?
- neuroprotective?

probably interferes with normal neuronal cell function

could directly or indirectly lead to neuronal cell death

neuronal degeneration and death occurs via apoptosis

mainly affects the striatum causing atrophy of putamen and caudate (caudate is first)

1st affects the **indirect pathway**

damaged striatal neurons exert less inhibition upon the external globus pallidus (GP)

GP increases inhibition of the subthalamic nuclei

subthalamic nuclei decrease excitation of internal globus pallidus (IGP)

IGP exerts less inhibition of thalamus

overstimulation of the motor cortex = **hyperkinetic movement disorder** characterized by irregular jerky movements or **chorea**

later affects the **direct pathway**

striatum decreases inhibition of internal globus pallidus (IGP)

IGP is able to exert more inhibition of thalamus

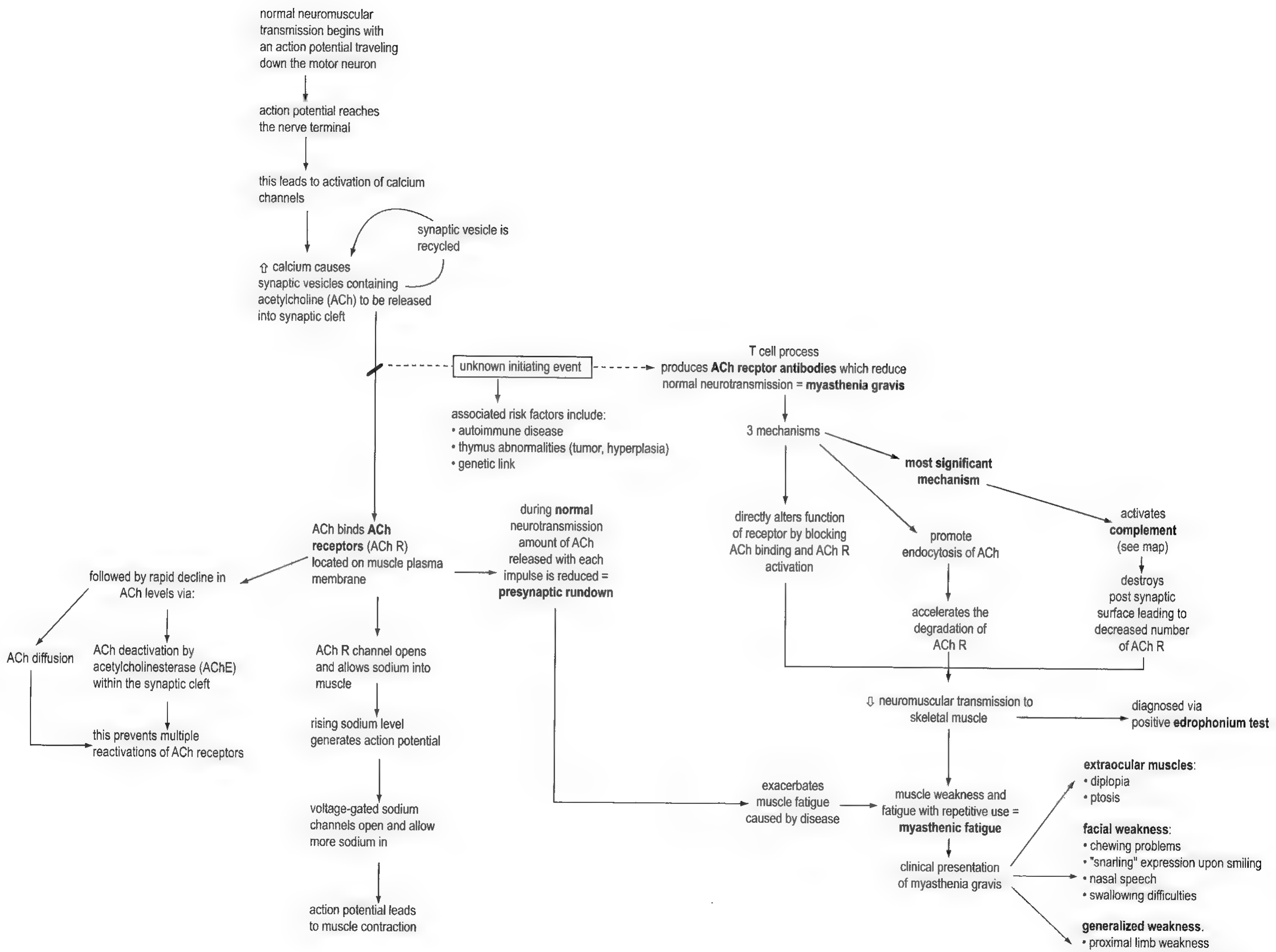
less stimulation of motor cortex

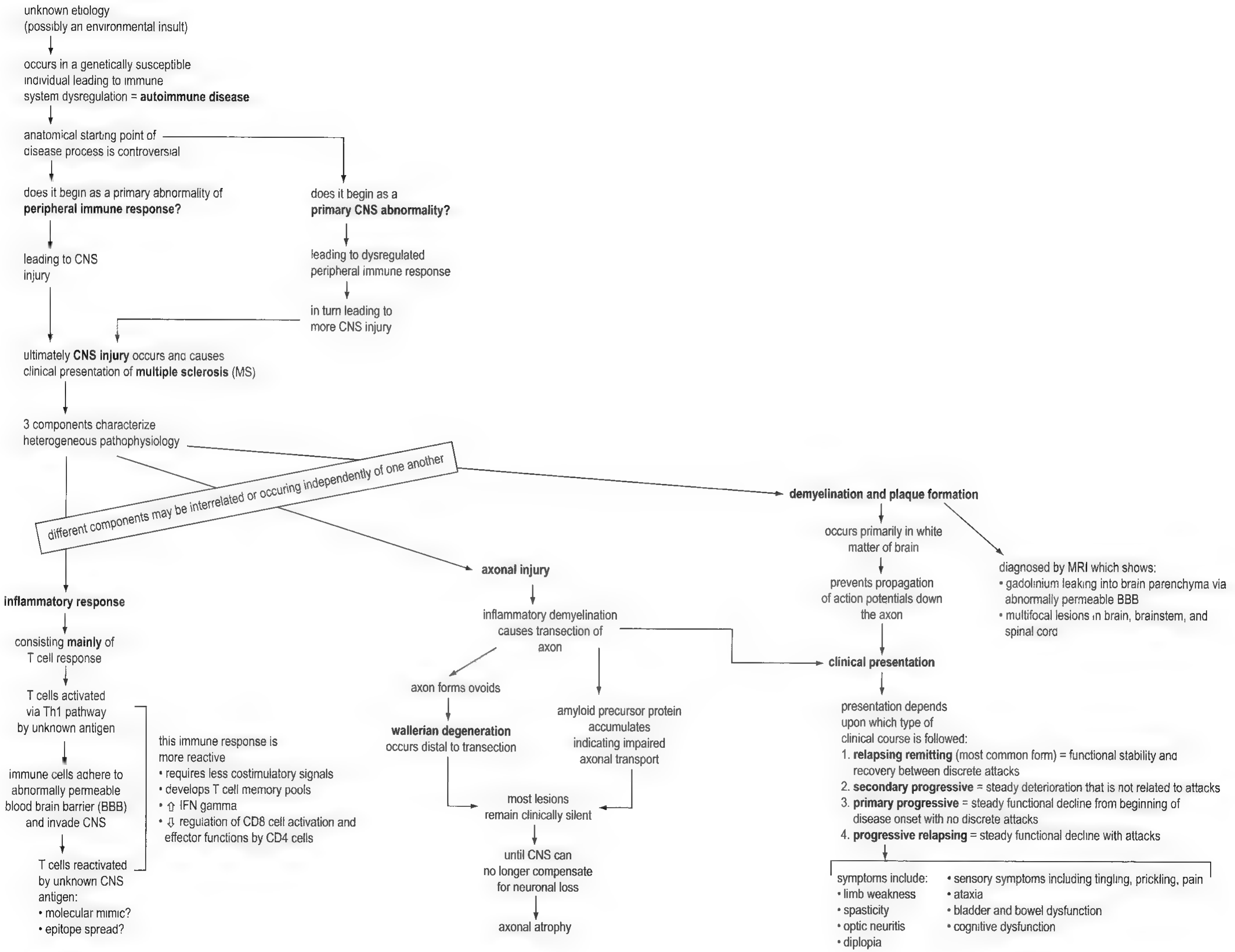
slowing down of motor movements = **athetosis**

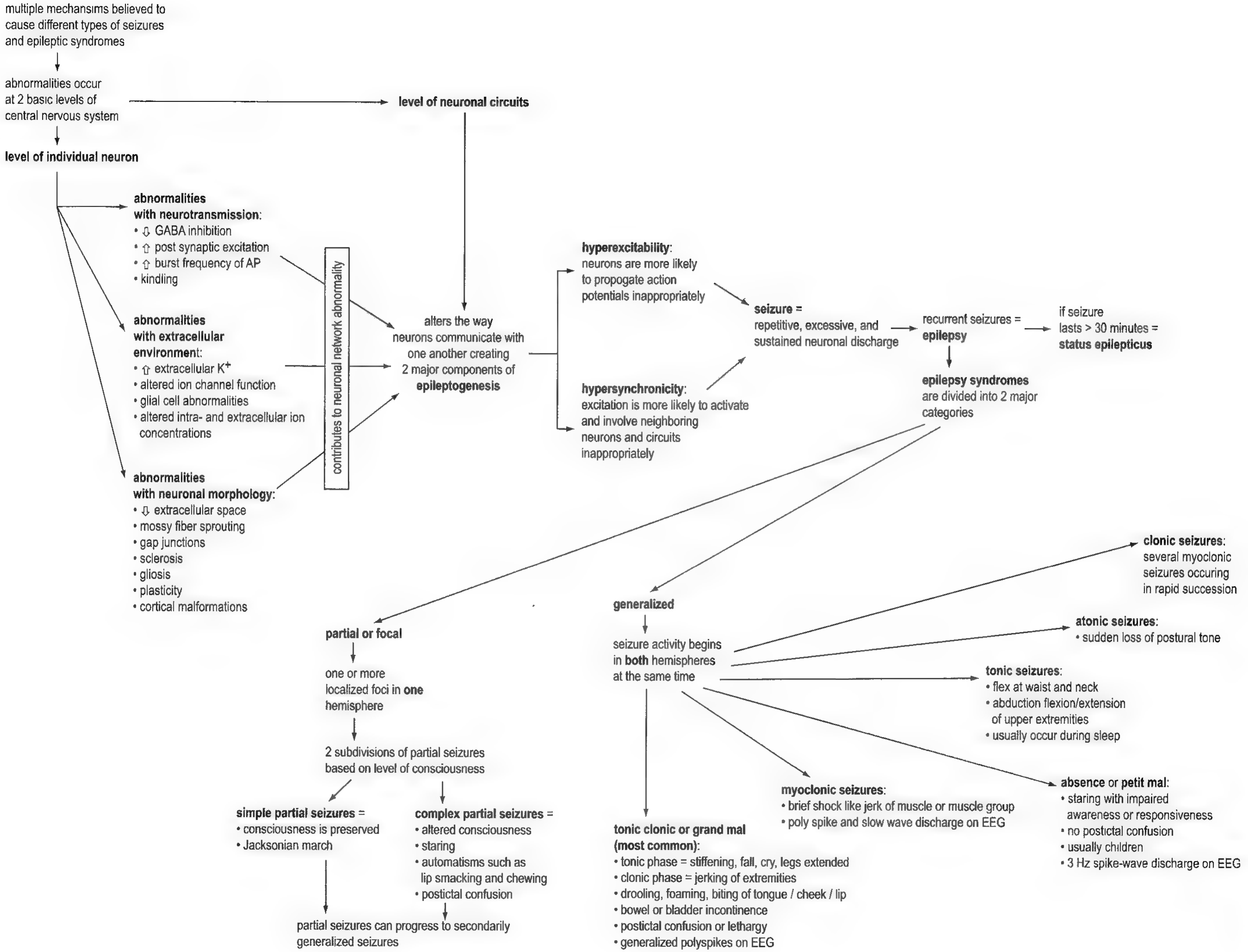
other signs and symptoms include:

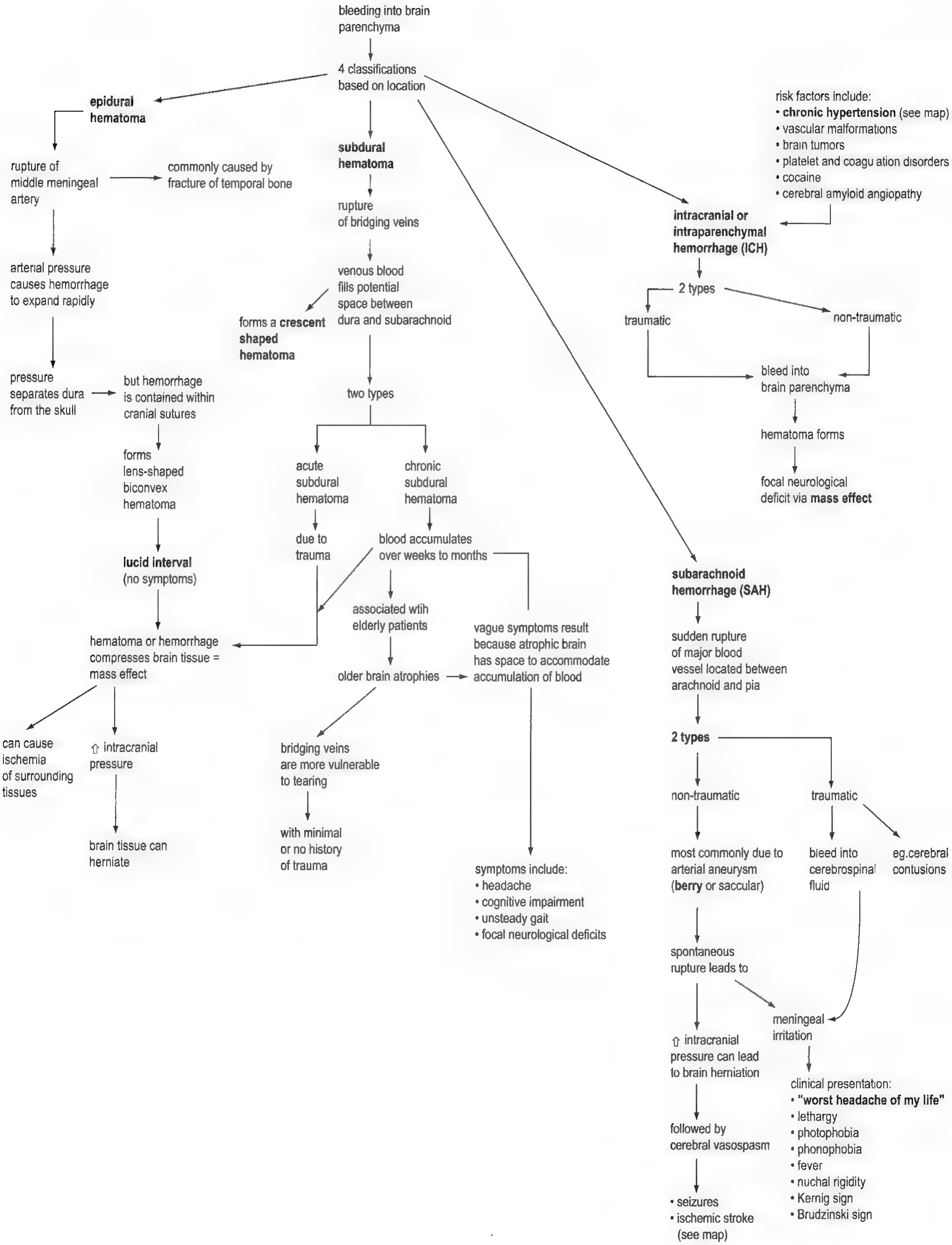
- clumsiness
- slow saccadic eye movements
- memory problems
- concentration problems
- depression
- paranoia
- hallucinations
- dementia

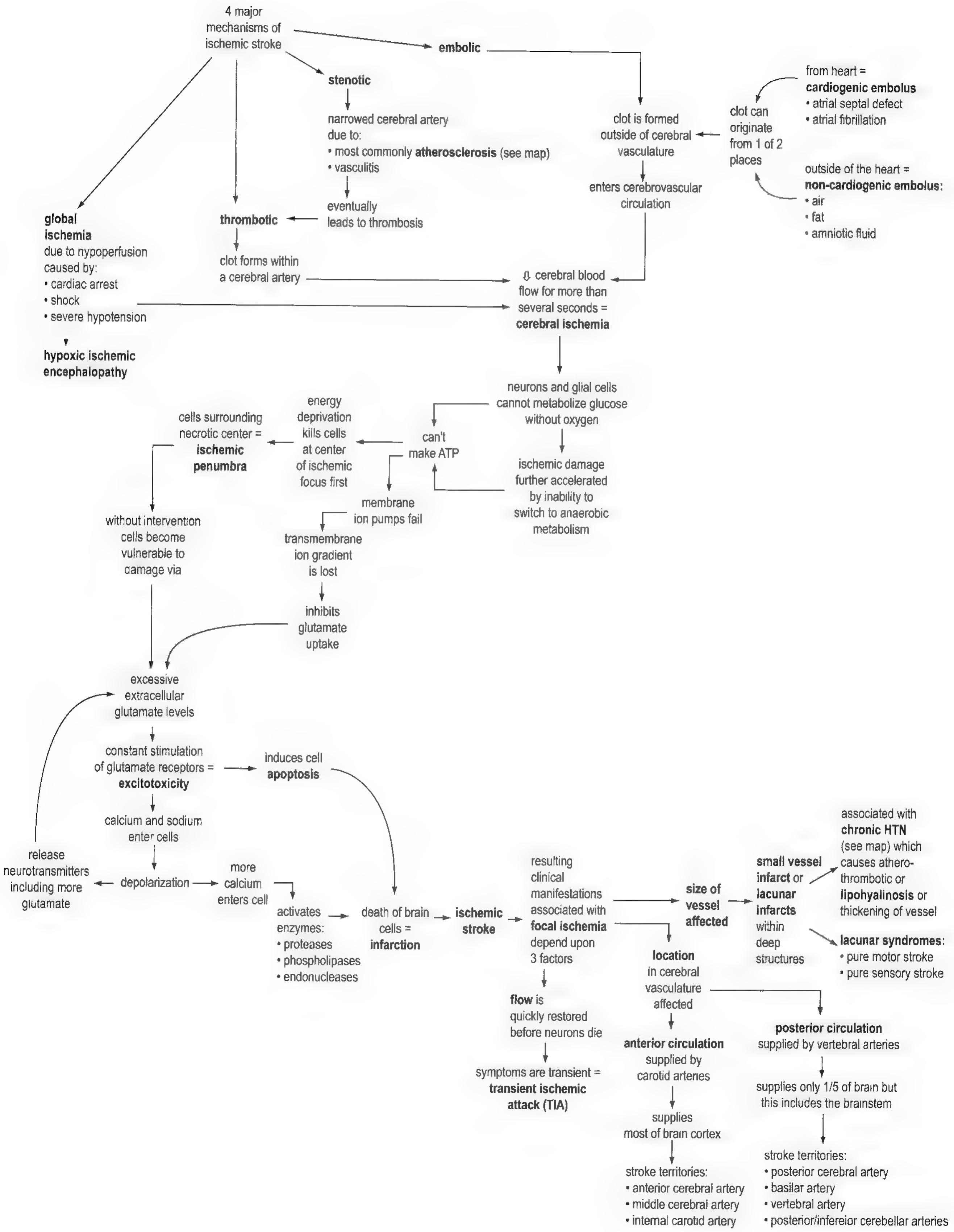
ultimately fatal due to aspiration pneumonia or suffocation secondary to dysphagia


normal neuromuscular transmission begins with an action potential traveling down the motor neuron
action potential reaches the nerve terminal
this leads to activation of calcium channels
⇧ calcium causes synaptic vesicles containing acetylcholine (ACh) to be released into synaptic cleft
synaptic vesicle is recycled
unknown initiating event
associated risk factors include:
• autoimmune disease
• thymus abnormalities (tumor, hyperplasia)
• genetic link
T cell process produces **ACh recptor antibodies** which reduce normal neurotransmission = **myasthenia gravis**
3 mechanisms
directly alters function of receptor by blocking ACh binding and ACh R activation
promote endocytosis of ACh
accelerates the degradation of ACh R
most significant mechanism
activates **complement** (see map)
destroys post synaptic surface leading to decreased number of ACh R
ACh binds **ACh receptors** (ACh R) located on muscle plasma membrane
during **normal** neurotransmission amount of ACh released with each impulse is reduced = **presynaptic rundown**
followed by rapid decline in ACh levels via:
ACh diffusion
ACh deactivation by acetylcholinesterase (AChE) within the synaptic cleft
this prevents multiple reactivations of ACh receptors
ACh R channel opens and allows sodium into muscle
rising sodium level generates action potential
voltage-gated sodium channels open and allow more sodium in
action potential leads to muscle contraction
⇩ neuromuscular transmission to skeletal muscle
diagnosed via positive **edrophonium test**
exacerbates muscle fatigue caused by disease
muscle weakness and fatigue with repetitive use = **myasthenic fatigue**
clinical presentation of myasthenia gravis
extraocular muscles:
• diplopia
• ptosis
facial weakness:
• chewing problems
• "snarling" expression upon smiling
• nasal speech
• swallowing difficulties
generalized weakness.
• proximal limb weakness
• **normal** deep tendon reflexes
• respiratory muscle weakness


unknown etiology
(possibly an environmental insult)
occurs in a genetically susceptible individual leading to immune system dysregulation = **autoimmune disease**
anatomical starting point of disease process is controversial
does it begin as a primary abnormality of **peripheral immune response?**
leading to CNS injury
does it begin as a **primary CNS abnormality?**
leading to dysregulated peripheral immune response
in turn leading to more CNS injury
ultimately **CNS injury** occurs and causes clinical presentation of **multiple sclerosis** (MS)
3 components characterize heterogeneous pathophysiology
different components may be interrelated or occuring independently of one another
inflammatory response
consisting **mainly** of T cell response
T cells activated via Th1 pathway by unknown antigen
immune cells adhere to abnormally permeable blood brain barrier (BBB) and invade CNS
T cells reactivated by unknown CNS antigen:
• molecular mimic?
• epitope spread?
this immune response is more reactive
• requires less costimulatory signals
• develops T cell memory pools
• ⇧ IFN gamma
• ⇩ regulation of CD8 cell activation and effector functions by CD4 cells
axonal injury
inflammatory demyelination causes transection of axon
axon forms ovoids
wallerian degeneration occurs distal to transection
amyloid precursor protein accumulates indicating impaired axonal transport
most lesions remain clinically silent
until CNS can no longer compensate for neuronal loss
axonal atrophy
demyelination and plaque formation
occurs primarily in white matter of brain
prevents propagation of action potentials down the axon
diagnosed by MRI which shows:
• gadolinium leaking into brain parenchyma via abnormally permeable BBB
• multifocal lesions in brain, brainstem, and spinal cord
clinical presentation
presentation depends upon which type of clinical course is followed:
1. **relapsing remitting** (most common form) = functional stability and recovery between discrete attacks
2. **secondary progressive** = steady deterioration that is not related to attacks
3. **primary progressive** = steady functional decline from beginning of disease onset with no discrete attacks
4. **progressive relapsing** = steady functional decline with attacks
symptoms include:
• limb weakness
• spasticity
• optic neuritis
• diplopia
• sensory symptoms including tingling, prickling, pain
• ataxia
• bladder and bowel dysfunction
• cognitive dysfunction


multiple mechansims believed to cause different types of seizures and epileptic syndromes
abnormalities occur at 2 basic levels of central nervous system
level of individual neuron
level of neuronal circuits
abnormalities with neurotransmission:
• ⇩ GABA inhibition
• ⇧ post synaptic excitation
• ⇧ burst frequency of AP
• kindling
abnormalities with extracellular environment:
• ⇧ extracellular K+
• altered ion channel function
• glial cell abnormalities
• altered intra- and extracellular ion concentrations
abnormalities with neuronal morphology:
• ⇩ extracellular space
• mossy fiber sprouting
• gap junctions
• sclerosis
• gliosis
• plasticity
• cortical malformations
contributes to neuronal network abnormality
alters the way neurons communicate with one another creating 2 major components of epileptogenesis
hyperexcitability: neurons are more likely to propogate action potentials inappropriately
hypersynchronicity: excitation is more likely to activate and involve neighboring neurons and circuits inappropriately
seizure = repetitive, excessive, and sustained neuronal discharge
recurrent seizures = epilepsy
if seizure lasts > 30 minutes = status epilepticus
epilepsy syndromes are divided into 2 major categories
partial or focal
one or more localized foci in one hemisphere
2 subdivisions of partial seizures based on level of consciousness
simple partial seizures =
• consciousness is preserved
• Jacksonian march
complex partial seizures =
• altered consciousness
• staring
• automatisms such as lip smacking and chewing
• postictal confusion
partial seizures can progress to secondarily generalized seizures
generalized
seizure activity begins in both hemispheres at the same time
tonic clonic or grand mal (most common):
• tonic phase = stiffening, fall, cry, legs extended
• clonic phase = jerking of extremities
• drooling, foaming, biting of tongue / cheek / lip
• bowel or bladder incontinence
• postictal confusion or lethargy
• generalized polyspikes on EEG
myoclonic seizures:
• brief shock like jerk of muscle or muscle group
• poly spike and slow wave discharge on EEG
clonic seizures: several myoclonic seizures occuring in rapid succession
atonic seizures:
• sudden loss of postural tone
tonic seizures:
• flex at waist and neck
• abduction flexion/extension of upper extremities
• usually occur during sleep
absence or petit mal:
• staring with impaired awareness or responsiveness
• no postictal confusion
• usually children
• 3 Hz spike-wave discharge on EEG


bleeding into brain parenchyma
4 classifications based on location
epidural hematoma
rupture of middle meningeal artery
commonly caused by fracture of temporal bone
arterial pressure causes hemorrhage to expand rapidly
pressure separates dura from the skull
but hemorrhage is contained within cranial sutures
forms lens-shaped biconvex hematoma
lucid interval (no symptoms)
hematoma or hemorrhage compresses brain tissue = mass effect
can cause ischemia of surrounding tissues
⇧ intracranial pressure
brain tissue can herniate
subdural hematoma
rupture of bridging veins
venous blood fills potential space between dura and subarachnoid
forms a **crescent shaped hematoma**
two types
acute subdural hematoma
due to trauma
chronic subdural hematoma
blood accumulates over weeks to months
associated wtih elderly patients
older brain atrophies
vague symptoms result because atrophic brain has space to accommodate accumulation of blood
bridging veins are more vulnerable to tearing
with minimal or no history of trauma
symptoms include:
• headache
• cognitive impairment
• unsteady gait
• focal neurological deficits
risk factors include:
• **chronic hypertension** (see map)
• vascular malformations
• brain tumors
• platelet and coagulation disorders
• cocaine
• cerebral amyloid angiopathy
intracranial or intraparenchymal hemorrhage (ICH)
2 types
traumatic
non-traumatic
bleed into brain parenchyma
hematoma forms
focal neurological deficit via **mass effect**
subarachnoid hemorrhage (SAH)
sudden rupture of major blood vessel located between arachnoid and pia
2 types
non-traumatic
traumatic
most commonly due to arterial aneurysm (**berry** or saccular)
bleed into cerebrospinal fluid
eg.cerebral contusions
spontaneous rupture leads to
meningeal irritation
⇧ intracranial pressure can lead to brain herniation
followed by cerebral vasospasm
• seizures
• ischemic stroke (see map)
clinical presentation:
• **"worst headache of my life"**
• lethargy
• photophobia
• phonophobia
• fever
• nuchal rigidity
• Kernig sign
• Brudzinski sign



4 major mechanisms of ischemic stroke

embolic

clot is formed outside of cerebral vasculature

clot can originate from 1 of 2 places

from heart = **cardiogenic embolus**
- atrial septal defect
- atrial fibrillation

outside of the heart = **non-cardiogenic embolus:**
- air
- fat
- amniotic fluid

enters cerebrovascular circulation

stenotic

narrowed cerebral artery due to:
- most commonly **atherosclerosis** (see map)
- vasculitis

eventually leads to thrombosis

thrombotic

clot forms within a cerebral artery

global ischemia due to hypoperfusion caused by:
- cardiac arrest
- shock
- severe hypotension

hypoxic ischemic encephalopathy

⇩ cerebral blood flow for more than several seconds = **cerebral ischemia**

neurons and glial cells cannot metabolize glucose without oxygen

ischemic damage further accelerated by inability to switch to anaerobic metabolism

can't make ATP

energy deprivation kills cells at center of ischemic focus first

cells surrounding necrotic center = **ischemic penumbra**

without intervention cells become vulnerable to damage via

membrane ion pumps fail

transmembrane ion gradient is lost

inhibits glutamate uptake

excessive extracellular glutamate levels

constant stimulation of glutamate receptors = **excitotoxicity**

induces cell **apoptosis**

calcium and sodium enter cells

depolarization

release neurotransmitters including more glutamate

more calcium enters cell

activates enzymes:
- proteases
- phospholipases
- endonucleases

death of brain cells = **infarction**

ischemic stroke

resulting clinical manifestations associated with **focal ischemia** depend upon 3 factors

flow is quickly restored before neurons die

symptoms are transient = **transient ischemic attack (TIA)**

size of vessel affected

small vessel infarct or **lacunar infarcts** within deep structures

associated with **chronic HTN** (see map) which causes atherothrombotic or **lipohyalinosis** or thickening of vessel

lacunar syndromes:
- pure motor stroke
- pure sensory stroke

location in cerebral vasculature affected

anterior circulation supplied by carotid arteries

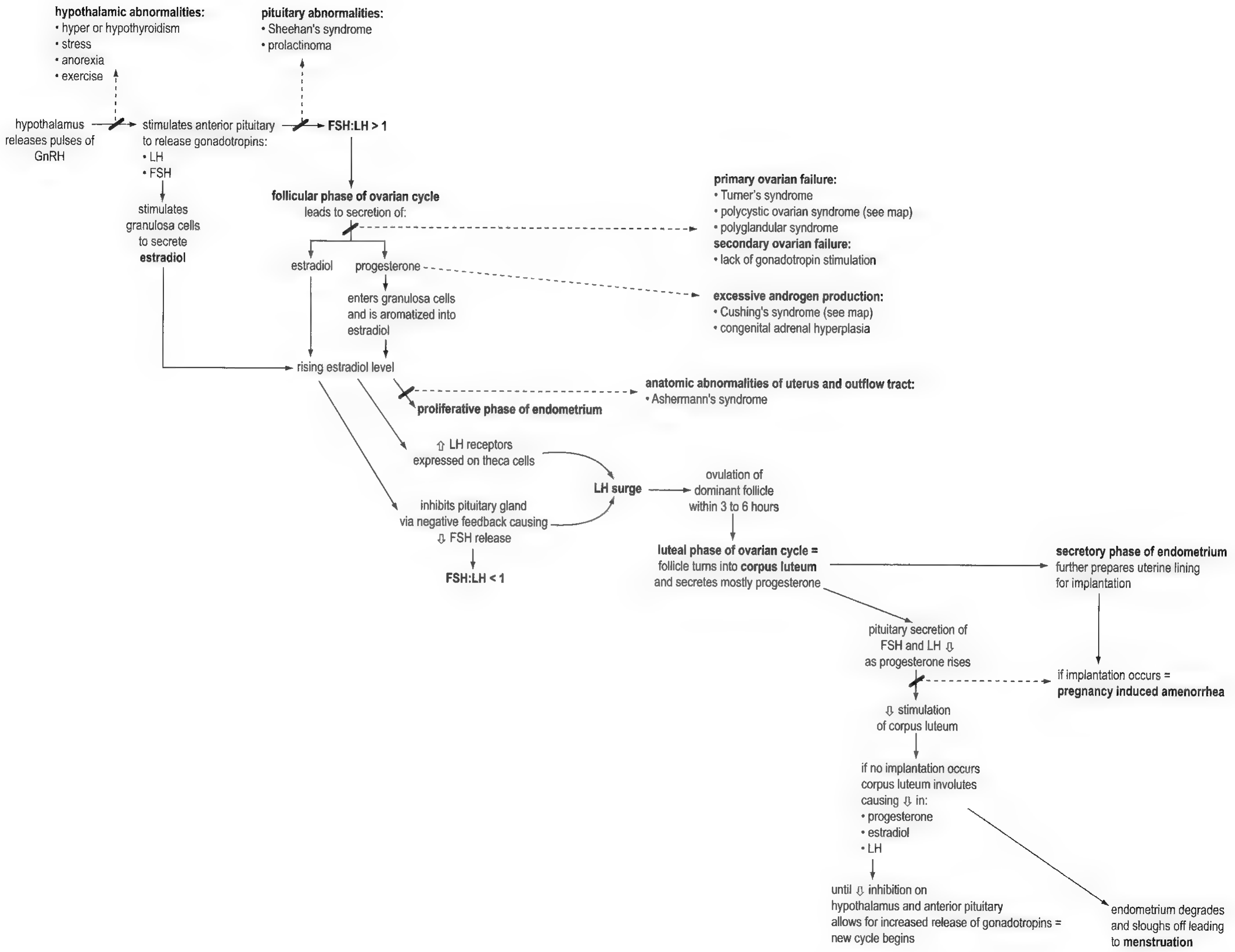
supplies most of brain cortex

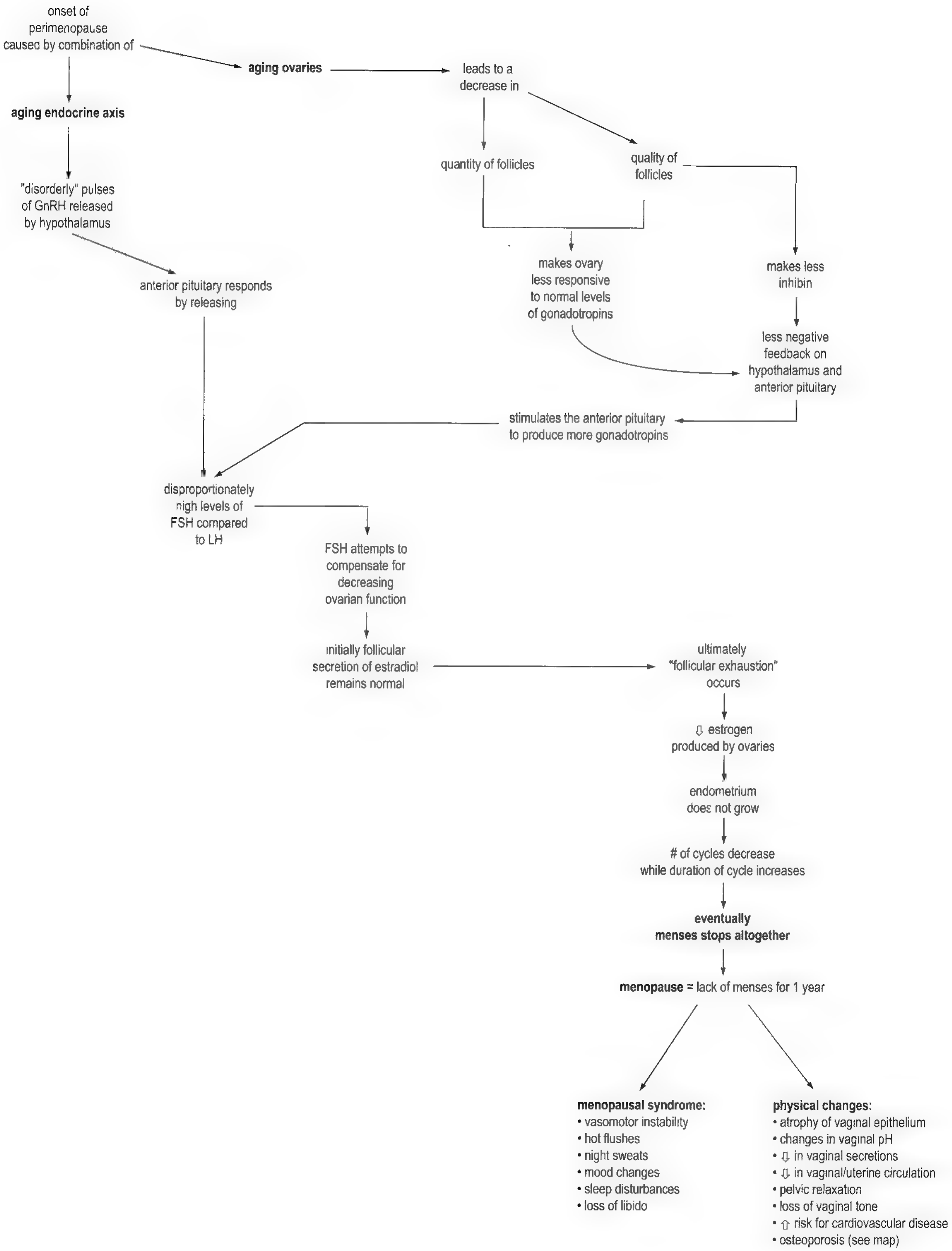
stroke territories:
- anterior cerebral artery
- middle cerebral artery
- internal carotid artery

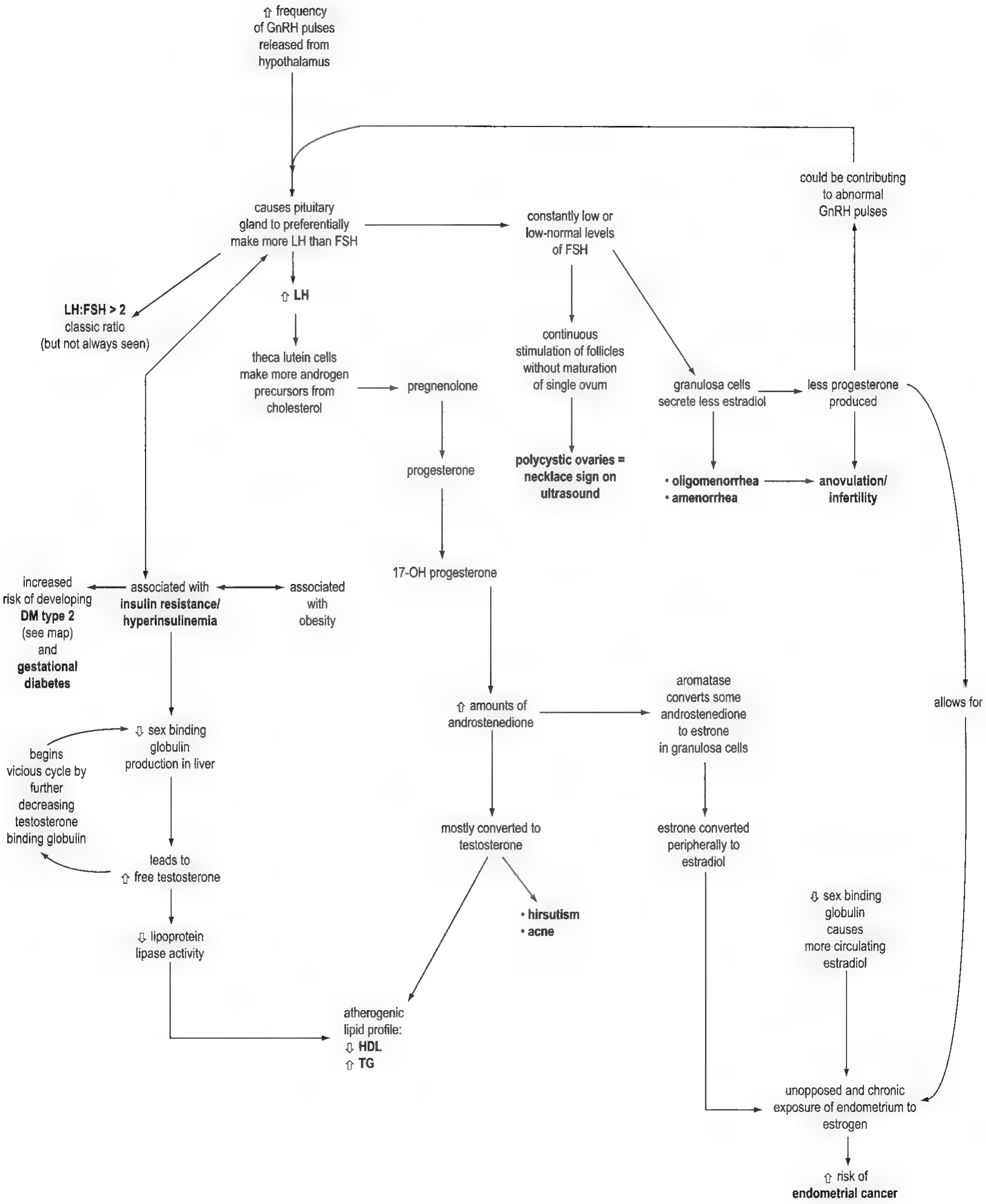
posterior circulation supplied by vertebral arteries

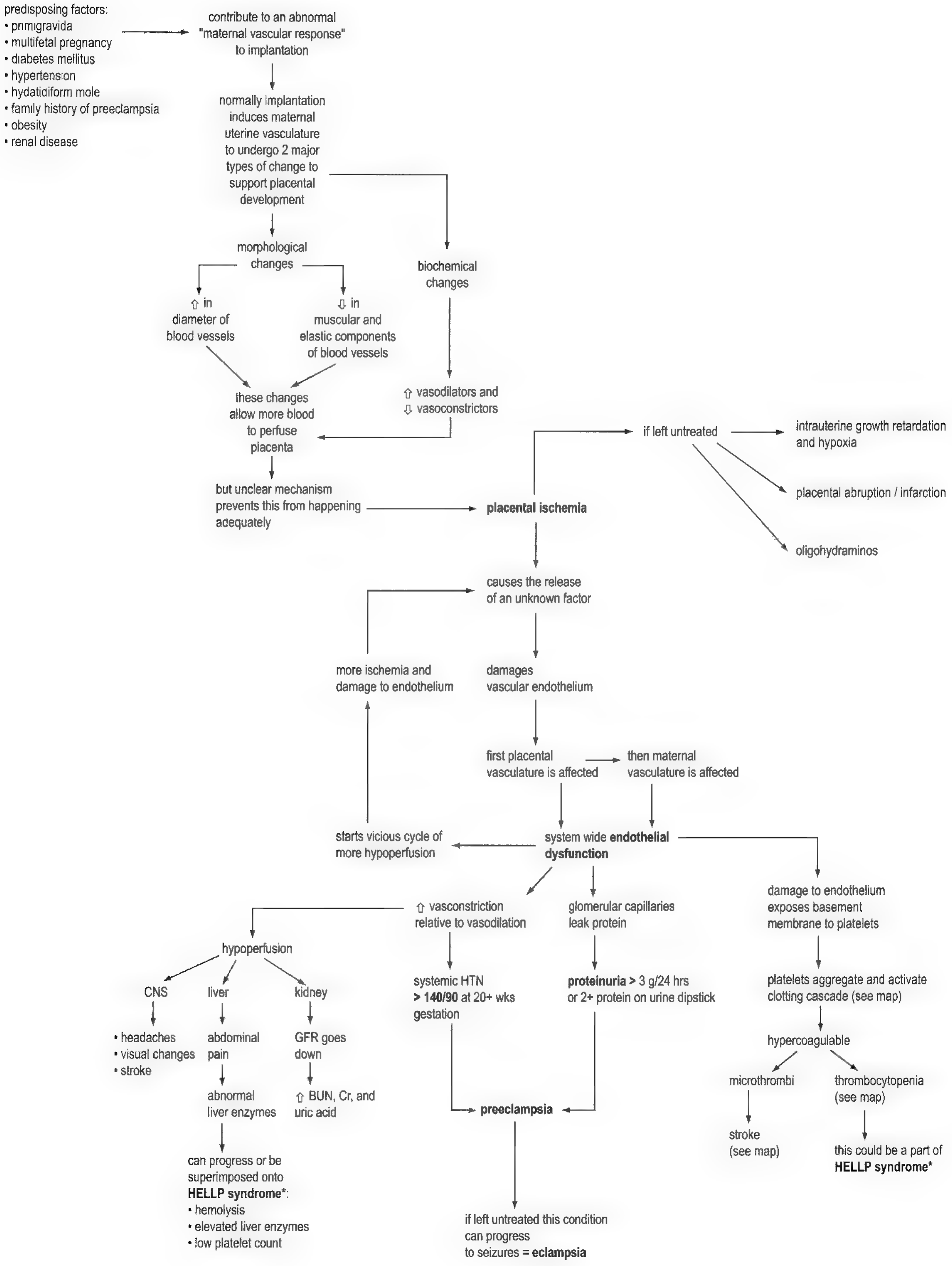
supplies only 1/5 of brain but this includes the brainstem

stroke territories:
- posterior cerebral artery
- basilar artery
- vertebral artery
- posterior/infereior cerebellar arteries


hypothalamic abnormalities:
• hyper or hypothyroidism
• stress
• anorexia
• exercise
pituitary abnormalities:
• Sheehan's syndrome
• prolactinoma
hypothalamus releases pulses of GnRH
stimulates anterior pituitary to release gonadotropins:
• LH
• FSH
FSH:LH > 1
stimulates granulosa cells to secrete estradiol
follicular phase of ovarian cycle leads to secretion of:
estradiol
progesterone
enters granulosa cells and is aromatized into estradiol
primary ovarian failure:
• Turner's syndrome
• polycystic ovarian syndrome (see map)
• polyglandular syndrome
secondary ovarian failure:
• lack of gonadotropin stimulation
excessive androgen production:
• Cushing's syndrome (see map)
• congenital adrenal hyperplasia
rising estradiol level
proliferative phase of endometrium
anatomic abnormalities of uterus and outflow tract:
• Ashermann's syndrome
⇧ LH receptors expressed on theca cells
inhibits pituitary gland via negative feedback causing ⇩ FSH release
FSH:LH < 1
LH surge
ovulation of dominant follicle within 3 to 6 hours
luteal phase of ovarian cycle = follicle turns into corpus luteum and secretes mostly progesterone
secretory phase of endometrium further prepares uterine lining for implantation
pituitary secretion of FSH and LH ⇩ as progesterone rises
if implantation occurs = pregnancy induced amenorrhea
⇩ stimulation of corpus luteum
if no implantation occurs corpus luteum involutes causing ⇩ in:
• progesterone
• estradiol
• LH
until ⇩ inhibition on hypothalamus and anterior pituitary allows for increased release of gonadotropins = new cycle begins
endometrium degrades and sloughs off leading to menstruation


onset of perimenopause caused by combination of
aging ovaries
leads to a decrease in
aging endocrine axis
quantity of follicles
quality of follicles
"disorderly" pulses of GnRH released by hypothalamus
makes ovary less responsive to normal levels of gonadotropins
makes less inhibin
anterior pituitary responds by releasing
less negative feedback on hypothalamus and anterior pituitary
stimulates the anterior pituitary to produce more gonadotropins
disproportionately high levels of FSH compared to LH
FSH attempts to compensate for decreasing ovarian function
initially follicular secretion of estradiol remains normal
ultimately "follicular exhaustion" occurs
⇩ estrogen produced by ovaries
endometrium does not grow
# of cycles decrease while duration of cycle increases
eventually menses stops altogether
menopause = lack of menses for 1 year
menopausal syndrome:
• vasomotor instability
• hot flushes
• night sweats
• mood changes
• sleep disturbances
• loss of libido
physical changes:
• atrophy of vaginal epithelium
• changes in vaginal pH
• ⇩ in vaginal secretions
• ⇩ in vaginal/uterine circulation
• pelvic relaxation
• loss of vaginal tone
• ⇧ risk for cardiovascular disease
• osteoporosis (see map)


⇧ frequency of GnRH pulses released from hypothalamus
causes pituitary gland to preferentially make more LH than FSH
constantly low or low-normal levels of FSH
could be contributing to abnormal GnRH pulses
LH:FSH > 2 classic ratio (but not always seen)
⇧ LH
theca lutein cells make more androgen precursors from cholesterol
pregnenolone
progesterone
17-OH progesterone
continuous stimulation of follicles without maturation of single ovum
polycystic ovaries = necklace sign on ultrasound
granulosa cells secrete less estradiol
less progesterone produced
• oligomenorrhea
• amenorrhea
anovulation/ infertility
increased risk of developing DM type 2 (see map) and gestational diabetes
associated with insulin resistance/ hyperinsulinemia
associated with obesity
⇧ amounts of androstenedione
aromatase converts some androstenedione to estrone in granulosa cells
allows for
⇩ sex binding globulin production in liver
begins vicious cycle by further decreasing testosterone binding globulin
leads to ⇧ free testosterone
mostly converted to testosterone
estrone converted peripherally to estradiol
• hirsutism
• acne
⇩ sex binding globulin causes more circulating estradiol
⇩ lipoprotein lipase activity
atherogenic lipid profile:
⇩ HDL
⇧ TG
unopposed and chronic exposure of endometrium to estrogen
⇧ risk of endometrial cancer


predisposing factors:
• primigravida
• multifetal pregnancy
• diabetes mellitus
• hypertension
• hydatidiform mole
• family history of preeclampsia
• obesity
• renal disease
contribute to an abnormal "maternal vascular response" to implantation
normally implantation induces maternal uterine vasculature to undergo 2 major types of change to support placental development
morphological changes
biochemical changes
⇧ in diameter of blood vessels
⇩ in muscular and elastic components of blood vessels
these changes allow more blood to perfuse placenta
⇧ vasodilators and ⇩ vasoconstrictors
but unclear mechanism prevents this from happening adequately
placental ischemia
if left untreated
intrauterine growth retardation and hypoxia
placental abruption / infarction
oligohydraminos
causes the release of an unknown factor
more ischemia and damage to endothelium
damages vascular endothelium
first placental vasculature is affected
then maternal vasculature is affected
starts vicious cycle of more hypoperfusion
system wide endothelial dysfunction
⇧ vasconstriction relative to vasodilation
glomerular capillaries leak protein
damage to endothelium exposes basement membrane to platelets
hypoperfusion
CNS
liver
kidney
• headaches
• visual changes
• stroke
abdominal pain
abnormal liver enzymes
can progress or be superimposed onto HELLP syndrome*:
• hemolysis
• elevated liver enzymes
• low platelet count
GFR goes down
⇧ BUN, Cr, and uric acid
systemic HTN > 140/90 at 20+ wks gestation
proteinuria > 3 g/24 hrs or 2+ protein on urine dipstick
preeclampsia
if left untreated this condition can progress to seizures = eclampsia
platelets aggregate and activate clotting cascade (see map)
hypercoagulable
microthrombi
thrombocytopenia (see map)
stroke (see map)
this could be a part of HELLP syndrome*

APPENDIX A

Normal blood (B), plasma (P), or serum (S) values

	Fluid	Reference Range	System International Reference Range
Alanine aminotransferase (ALT)	S	8–20 U/L	0.13–0.33 kat/L
Aldosterone, with normal sodium intake of 100–200 mEq/day	S	Supine: <16 ng/dL	<444 pmol/L
		Upright: 4–31 ng/dL	111–860 pmol/L
Arginine vasopressin	P	1.0–13.3 pg/mL	1.0–13.3 ng/L
Aspartate aminotransferase (AST)	S	9–40 U/L	0.15–0.67 kat/L
Bicarbonate, arterial	P	22–26 mEq/L	22–26 mmol/L
Bilirubin, total	S	0.1–1.0 mg/dL	2–17 mol/L
Calcium	S	8.4–10.2 mg/dL	2.1–2.6 mmol/L
Carbon dioxide (PCO_2), arterial	B	35–45 mm Hg	4.7–6.0 kPa
Chloride	P, S	95–105 mEq/L	95–105 mmol/L
Cholesterol, recommended	S	<200 mg/dL	<5.2 mmol/L
Cortisol	S	0800 h: 5–23 g/dL	138–635 nmol/L
		1600 h: 3–15 g/dL	82–413 nmol/L
		2000 h: <50% of 0800 h value	<0.50 of 0800 h value
Creatine kinase	S	Female: 10–70 U/L	0.17–1.17 kat/L
		Male: 25–90 U/L	0.42–1.50 kat/L
Creatinine	S	0.6–1.2 mg/dL	53–106 mol/L
1,25-Dihydroxyvitamin D	S	16–42 pg/mL	38–101 pmol/L
25-Hydroxyvitamin D	S	8–80 ng/mL	20–200 nmol/L
Estradiol	P, S	Female	
		Prepubertal: <20 pg/mL	<73 pmol/L
		Premenopausal adult: 23–361 pg/mL	84–1325 pmol/L
		Postmenopausal adult: <30 pg/mL	<110 pmol/L
		Male: <50 pg/mL	<184 pmol/L
Ferritin	S	Male: 15–200 ng/mL	15–200 g/L
		Female: 12–150 ng/mL	12–150 g/L
Follicle-stimulating hormone	S	Male: 4–25 mIU/mL	4–25 U/L
		Female:	
		Premenopause: 4–30 mIU/mL	4–30 U/L
		Midcycle peak: 10–90 mIU/mL	10–90 U/L
		Postmenopause: 40–250 mIU/mL	40–250 U/L
Glucagon	P	50–200 pg/mL	50–200 ng/L
Glucose	S	Fasting: 70–110 mg/dL	3.9–6.1 mmol/L
		2-h postprandial: <140 mg/dL	<7.8 mmol/L

	Fluid	Reference Range	System International Reference Range
Growth hormone	P	2.0–6.0 ng/mL	2.0–6.0 g/L
HDL cholesterol, as major risk factor	S	<35 mg/dL	<0.91 mmol/L
Insulin	S	0–29 U/mL	0–208 pmol/L
Iron	S	50–170 g/dL	9–30 mol/L
Lactate dehydrogenase	S	100–190 U/L	1.7–3.2 kat/L
LDL cholesterol, desirable	S	<130 mg/dL	<3.36 mmol/L
Luteinizing hormone	S	Male: 6–23 mIU/mL	6–23 U/L
		Female	
		Follicular phase: 5–30 mIU/mL	5–30 U/L
		Midcycle: 75–150 mIU/mL	75–150 U/L
		Postmenopause: 30–200 mIU/mL	30–200 U/L
Magnesium	S	1.5–2.0 mEq/L	0.75–1.0 mmol/L
Osmolality	P, S	275–295 mosm/kg H_2O	275–295 mosm/kg H_2O
Oxygen content, arterial	B	17–21 mL/dL	0.17–0.21 L/L
Oxygen saturation, arterial	B	96–100%	0.96–1.00 mol/mol
Oxygen tension (PO_2), arterial	B	75–100 mm Hg	10.0–13.3 kPa
Parathyroid hormone	P	10–60 pg/mL	10–60 ng/L
pH, arterial	B	7.35–7.45	$[H^+]$ 35–45 nmol/L
Phosphatase, alkaline	S	20–70 U/L	0.33–1.17 kat/L
Phosphorus, inorganic	S	3.0–4.5 mg/dL	1.0–1.5 mmol/L
Potassium	S	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Prolactin	S	Female	
		Nonpregnant: 3–30 ng/mL	3–30 g/L
		Pregnant: 10–209 ng/mL	10–209 g/L
		Postmenopausal: 2–20 ng/mL	2–20 g/L
		Male: 2–18 ng/mL	2–18 g/L
Proteins			
Total	S	6.0–7.8 g/dL	60–78 g/L
Albumin	S	3.5–5.5 g/dL	35–55 g/L
Globulin	S	2.3–3.5 g/dL	23–35 g/L
Sodium	S	136–145 mEq/L	136–145 mmol/L
Testosterone, total, morning	P	Male: 300–1100 ng/dL	10.4–38.1 nmol/L
		Female: 20–90 ng/dL	0.7–3.1 nmol/L
Thyroid-stimulating hormone	S	0.5–5.0 U/mL	0.5–5.0 mU/L
Thyroxine (T_4), total	S	5–12 g/dL	64–155 nmol/L
Triglycerides, fasting	S	35–160 mg/dL	0.4–1.8 mmol/L
Triiodothyronine (T_3)	S	115–190 ng/dL	1.8–2.9 nmol/L
Urea nitrogen (BUN)	S	7–18 mg/dL	2.5–6.4 mmol urea/L
Uric acid	S	3.0–8.2 mg/dL	0.18–0.49 mmol/L

Hematologic values

Blood volume	Male: averages 69 mL/kg body weight Female: averages 65 mL/kg body weight	
Plasma volume	Male: 25–43 mL/kg body weight Female: 28–45 mL/kg body weight	0.025–0.043 L/kg body weight 0.028–0.045 L/kg body weight
Erythrocyte count	Male: 4.3–5.9 H 10^6/mm^3 Female: 3.5–5.5 H 10^6/mm^3	4.3–5.9 H 10^{12}/L 3.5–5.5 H 10^{12}/L
Erythrocyte sedimentation rate	Male: 0–15 mm/h Female: 0–20 mm/h	0–15 mm/h 0–20 mm/h
Hematocrit	Male: 41–53% Female: 36–46%	0.41–0.53 0.36–0.46
Hemoglobin, blood	Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL	2.09–2.71 mmol/L 1.86–2.48 mmol/L
Hemoglobin A_{1c}	#6% of total Hb	#0.06 of total Hb
Leukocyte count and differential		
Leukocyte count	4500–11,000/mm^3	4.5–11.0 H 10^9/L
Segmented neutrophils	45–74%	0.45–0.74
Bands	0–4%	0.00–0.04
Eosinophils	0–7%	0.00–0.07
Basophils	0–2%	0.00–0.02
Lymphocytes	16–45%	0.16–0.45
Monocytes	4–10%	0.04–0.10
Mean corpuscular hemoglobin	25.4–34.6 pg/cell	0.39–0.54 fmol/cell
Mean corpuscular hemoglobin conc.	31–36 g/dL	4.81–5.58 mmol Hb/L
Mean corpuscular volume	80–100 m^3	80–100 fL
Partial thromboplastin time, activated	25–40 seconds	25–40 seconds
Platelet count	150,000–400,000/mm^3	150–400 H 10^9/L
Prothrombin time	11–15 seconds	11–15 seconds
Red cell distribution width	11.5–14.5%	0.115–0.145
Reticulocyte count	0.5–1.5% of red cells	0.005–0.0015

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